Products for Tobacco Exposure Reduction

Several tobacco related products have been introduced recently with potential exposure reduction properties. Two classes of pharmacutical products approved for smoking cessation are also potential exposure reduction products. The chapter describes these products and concludes with a review of regulatory strategies currently in place.

TOBACCO AND TOBACCO PRODUCTS

At first glance, cigarettes seem very simple in construction and design. Typical cigarettes contain a tobacco blend, flavorings and other additives, filters, and cigarette paper. The impression of simplicity of cigarette construction wanes as each component is taken into consideration. There are various combinations of tobacco blends, filter types, and ventilation methods. Manufacturers have used various means of modifying their products to capture and shape the smokers' preference and acceptability of popular brands. Some modifications have had the potential for harm reduction. This section describes current tobacco products, including the curing and processing of tobacco, design features (both historical and contemporary) with exposure reduction potential, and currently available potential reduced-exposure products (PREPs).

Conventional Tobacco Products

There are a wide variety of tobacco products in the United States including cigarettes, cigars, cigarillos, bidis, kreteks, and different types of smokeless tobacco. The most common form of a tobacco product in the United States is the manufactured cigarette. A cigarette is considered to be any roll of tobacco wrapped in paper or in any substance not containing tobacco. Cigarettes can be either manufactured or individually constructed. Cigarettes are lit, and the burning process allows smoke to be inhaled at the other end. Cigarettes are approximately 8 mm in diameter and 70 mm to 100 mm in length.

A cigar is any roll of tobacco wrapped in leaf tobacco or in any substance containing tobacco. There are four main types of cigars: little cigars, small cigars (sometimes called cigarillos), regular cigars, and premium cigars. Little cigars contain air-cured and fermented tobaccos. Little cigars are wrapped either in reconstituted tobacco or in cigarette paper that contains tobacco and/or tobacco extract. Some little cigars have cellulose acetate filter tips and are shaped like cigarettes. Cigarillos are small, narrow cigars with no cigarette paper or acetate filter. Regular cigars are available in various shapes and sizes and rolled to a tip at one end. The dimensions vary from 110 to 150 mm in length and up to 17 mm in diameter. Regular cigars weigh between 5 and 17 grams. Premium cigars vary in size, ranging from 12 to 23 mm in diameter and 12.7 to 21.4 cm in length.

Bidis are made by rolling dried leaf into a conical shape around approximately 0.2 grams of sun-dried, flaked tobacco and securing the roll with a thread. Bidis are used extensively in India, the rural areas of several countries in Southeast Asia, and some parts of the United States. There have been no scientific studies or assessments of the physical characteristics and pharmacologic properties of Indian bidis. In comparison, American versions of bidis were shown to have higher percentages of tobacco by weight (94% vs. 42.5% respectively) and lower levels of nicotine (16.6 mg/g vs. 21.2 mg/g) than Indian bidis (Malson, 2000). Kreteks are a type of small cigar containing tobacco, cloves, and cocoa, which gives a characteristic flavor and 'honey' taste to the smoke. Kreteks are indigenous to Indonesia but are also available in the United States.

Smokeless tobacco includes tobacco that is sniffed, dipped, or chewed according to the type and constitution of the tobacco. Smokeless tobacco products are made from dark or burley-leaved tobacco. Smokeless tobacco is often referred to as oral tobacco or spit tobacco.

Snuff is a cured, finely ground, flavored tobacco product that is sold in tins or cans and is available in two main types: dry and moist. Dry snuff is fire-cured powdered tobacco and is sniffed. After initial curing, the tobacco is fermented further and processed into a dry powdered form. It has a moisture content of less than 10%. Moist snuff is a granulated tobacco product that is made from both air-cured and fire-cured tobacco and multiple additives. Moist snuff is used by placing a pinch or ('dip') between the lip or cheek and gum. Moist snuff consists of tobacco stems and leaves that are processed into fine particles or strips. It has a moisture content of up to 50%. It is sold in both loose form and ready-to-use pouches (also called packets or sachets) that contain about 0.5 grams tobacco. Moist snuff is available in two varieties, according to the size and consistency of the tobacco: long cut and fine cut. Moist snuff is by far the more prevalent form of snuff used in the United States.

Chewing tobacco is a coarsely shredded, flavored tobacco that is sold in pouches of tobacco leaves or in "plug" or "twist" form. Chewing tobacco is chewed or held in the cheek or lower lip.

Curing, Blending, and Processing

The genus *Nicotiana* is indigenous to the Americas. A member of the family Solanaceae, *Nicotiana* contains more than 64 species. In the United States, the tobacco used in cigarettes, cigars, and smokeless products comes from the species *N. tabacum* and can be categorized by the three traditional methods used in curing or by the geographic region in which it is grown. These are distinguished by important differences in sugar, nicotine, and nitrogen content (Browne, 1990).

Flue curing uses high heat to speed the curing process and control humidity. The principal chemical change is conversion of starch to sugars. During the aging of cured tobacco, enzymatic oxidation of amino acids and carbohydrates takes place. The water content, acidity, and concentration of malic and citric acids increase. There are other, undefined chemical changes that occur, resulting in increased aroma and a less bitter taste. Flue-cured tobacco is also called Bright (also known as Virginia) tobacco. These plants are grown in sandy soils from Virginia to Florida, but their agriculture is centered in North Carolina. These tobaccos generally have low nitrogen, high sugar content. The smoke from Bright is acidic with a light aroma. Bright tobacco has medium nicotine content.

Air curing uses heat only to maintain temperature and humidity, not to speed the curing process. The primary chemical changes that occur during air curing are protein degradation, polyphenol formation, and a change in the composition of organic acids. Air-cured tobacco consists of

Burley and Maryland tobacco. These plants are grown in silt loams in Kentucky, Tennessee, and western North Carolina and in sandy loam soils in southern Maryland. These tobaccos have very low sugar content and are more heavily fertilized with manure and artificial fertilizer than the flue-cured products. Air-cured tobaccos have an alkaline smoke, fuller aroma, and high nicotine content. Maryland tobacco also has the quality of continuing to burn on its own, making it less likely to self-extinguish.

Sun-cured or oriental tobaccos (Oriental) require a Mediterranean climate and come mostly from Turkey, Greece, Yugoslavia, Bulgaria, and Russia. They are cultivated with little fertilizer. Oriental tobaccos have mild, aromatic smoke and low nicotine content.

Cigarettes, cigars, and smokeless products use blended tobaccos. The largest component of most cigarette blends in the United States is Bright tobacco (Browne, 1990). Blends are made to achieve specific pH, taste, burning characteristics, and nicotine content. The type of tobacco blend found in cigarettes significantly affects the pH, nicotine content, and toxicity of the smoke produced. The blend can be manipulated by a choice of 60 species and 100 varieties of tobacco. Almost all commercial tobacco products, however, use N. tabacum species and a small amount of N. rustica in some specialized tobacco products. Cured tobacco lines can contain between 0.2 and 4.75% nicotine (depending on plant genetics, growing conditions, and place of harvest from the stalk; NIH, 1996).

In addition to tobacco leaf, reconstituted sheet tobacco is also used in most commercial products. Cigarettes primarily made with reconstituted tobacco deliver lower smoke yields of tar, phenols, and benzo [a] pyrene (NIH, 1996), Reconstituted tobacco sheet is also used for economic reasons and for the introduction of additives that change various characteristics of the cigarette. Reconstituted tobacco results from a process that combines stems, leaves, and tobacco scrap into a slurry or from making a tobacco "paper", which is cut (Browne, 1990).

Another alternative to leaf tobacco is puffed, expanded, or freeze-dried tobacco (NIH, 1996; Hoffman and Hoffman, 97). Less tobacco is therefore needed to fill a cigarette while still providing a sensation of fullness and substance in the smoke. While tobacco is being cured, it loses some of its integrity through water loss. Expanding tobacco increases its filling capacity in the final tobacco column of the cigarette by primarily restoring the original cellular structure. This process is performed by expanding the cells with water, steam, and various organic or inorganic fluids depending on the manufacturers patent (David and Nielsen, 1999; NIH, 1996).

The pH strongly influences the concentration of free nicotine in tobacco smoke. The pH is influenced by the type of tobacco used, as well as by the addition of ammonia to the manufacturing process. Free nicotine has a greater effect on the sensory nerves in the mouth and throat than protonated nicotine, which contributes to the impact or strength of the cigarette. Free nicotine is absorbed more rapidly than protonated nicotine across mucous membranes. The phenomenon of more rapid absorption of nicotine at higher pH has been documented in people using different brands of smokeless tobacco. Free nicotine is absorbed through the mouth from alkaline pipe, cigar, and dark cigarette smoke, but not from acidic smoke of blonde tobacco cigarettes. Free nicotine may be absorbed more quickly from the lungs of cigarette smokers as well, although this has not yet been demonstrated experimentally in smokers.

The nitrate content influences the carcinogenic potential of smoke. Nitrogen oxides formed during pyrolysis are free-radical precursors of the polycyclic aromatic hydrocarbons (PAHs). As nitrate concentration in tobacco increases, the synthesis of benzo[a]pyrene, a carcinogen, is inhibited. Air-cured tobaccos have higher content of nitrates than sun-cured or flue-cured tobaccos

and, therefore, lower BaP content. However, the higher the nitrate concentration, the higher are the levels of tobacco specific-nitrosamines (TSNAs), also a known carcinogen.

Hundreds of additives are used in the manufacturing of cigarettes. Several additives are known to have toxic properties. For example, glycerol is a humectant used in cigarettes. Glycerol may lead to the formation of acrolein, a ciliotoxic agent, and diethylene glycol can be converted to ethylene oxide, a carcinogenic compound (Hoffmann and Hoffmann, 1997). Eclipse™, that heats but does not burn tobacco, uses glycerol particles as the carrier for nicotine. The glycerol level in smoke from this product is much higher than in conventional low-yield products. As described above, some additives can influence other tobacco constituents (e.g., the role of ammonia in nicotine protonation and TSNA formation).

Although some additives have toxic potential, the concentration of these compounds is low (other than those listed above) and their relative contribution to overall toxicity compared to compounds such as TSNA, BaP, and carbon monoxide (CO) is not definitively known. The toxicity of individual ingredients is sometimes well described, but little is known about how toxicants affect the body when smoked in combination (U.S. DHHS, 2000). The current emphasis on additive disclosure focuses on the consumer's right to know and on understanding better which additives are used to increase the acceptability (e.g., by improving taste and smoothness) of the product to the consumer.

Menthol is a common additive used for flavor and customer acceptability. Early advertisements for menthol products claimed a "soothing" effect on irritated throats. Menthol can be added to cigarettes in several ways including addition to the tobacco shred through an ethanol spray and addition to the filter or packaging. Approximately 3 mg of menthol is added per cigarette. The rest is lost through the filter, sidestream smoke, and in packaging (Browne, 1990). Because menthol is an anesthetizing agent, it has been hypothesized that it may be easier to inhale deeper when smoking a mentholated cigarette. This might also help explain why there are higher rates of lung cancer among blacks despite their lower daily cigarette consumption than whites, who tend not smoke mentholated cigarettes. Various studies, however, have produced mixed results on the subject (McCarthy et al., 1995; "Women who smoke menthol cigarettes have greater nicotine exposure, Oncology, 1999; Kabat and Hebert, 1991; Carpenter et al., 1999; Gaworski et al., 1997; Clark et al., 1996; Sidney et al., 1995).

Cigarette paper is second to tobacco as the most variable component in producing cigarettes. The degree of ventilation allowed by the paper can be manipulated in the production process. More porous cigarette paper has been shown to reduce smoke yields of CO and tar as well as volatile nitrosamines, TSNAs, and BaP through dilution. Increased permeability does not reduce the low-molecular-weight gas-phase components in smoke however (NIH, 1996). For a more detailed discussion of the toxicology of smoke, see Chapter 10.

A new paper has been introduced for Merit™ cigarettes, which claimed to decrease the smoldering of cigarettes when dropped onto fabric. The new technology consists of a modified wrapping paper that reduces the amount of oxygen entering the cigarette, therefore slowing the rate at which it burns. This could decrease the 25% of fatal residential fires started by smoldering cigarettes (Meier, 2000). New York became the first state to pass legislation imposing fire safety standards on cigarettes (Cigarettes-fire bill, 2000).

Smoke Yields

The procedure for measuring the tar and nicotine yields of mainstream smoke (i.e., the "smoking machine") is standardized for consistency between laboratories and from product to product. There are two methods in widespread use: the Federal Trade Commission (FTC) method and the International Standards Organization (ISO) method. Differences between these two are minor, and puff volume, duration, and interval are common to both standards. Particulate matter is collected on Cambridge filter pads as what is called "wet total particulate matter" (Davis and Nielson, 1999). Tar is a generic term for the total particulate matter minus the nicotine and water. The material that passes through the filter is called the vapor phase. This is described in more detail in Chapters 10 and 11.

Tar yields are influenced primarily through filtration, ventilation (tip ventilation holes and paper porosity), and the choice of tobacco processing and blend. As with any agricultural product, there is natural variation from year to year. In the interest of manufacturing a consistent product, prepared tobacco is blended with stock of crops from previous years to maintain a uniform product line. Finally, the burn rate of cigarettes has been proven to influence smoke yields. The faster the burn rate, the lower the tar yields will be, according to FTC measurements. Shredded tobacco can facilitate a faster burn rate (Davis and Nielsen, 1999), as can the use of accelerants.

The FTC test does not account for the wide range of smoking behaviors and compensation that occurs naturally among smokers, thus, the standardization has come under great criticism. Human smoking behavior can greatly influence the tar, nicotine, and CO levels to which smokers are exposed. The yields of so-called light and ultralight cigarettes have changed over the years but have produced similar nicotine levels across yields. These terms are not official government designates and are often part of the trademarked name of a product. In general, however, ultralights have less than 6 mg of tar, light cigarettes have between 6 and 15 mg of tar, and "regular or full-flavored" cigarettes have more than 15 mg (NIH, 1996; Sweeney et al., 1999). Although there is not a standard nicotine classification, a study by Byrd et al. (1995) comparing measured and FTC-predicted nicotine uptake in smokers described nicotine levels in products they categorized as 1 mg tar, ultralow tar, full-flavor low tar, and full-flavor cigarettes. The mean FTC nicotine yields were 0.14, 0.49, 0.67, and 1.13 mg per cigarette, respectively. FTC measures, particularly for low-tar cigarettes or for cigarettes with filter ventilation holes, do not, however, reflect true exposures in humans. Cigarettes are positioned in the smoking machines in a manner that allows air to enter the perforated filters. These holes are often covered by the lips or fingers of smokers (Hoffman and Hoffman, 1997). In addition, smokers of low-yield products compensate by inhaling more deeply, holding a puff in the lungs for longer periods, or puffing more frequently.

Conventional and Historical PREP Technology

Two cigarette design features that reduce toxin yields as measured by the FTC are dilution and filtration. Dilution is achieved primarily with ventilation, although paper porosity can also increase smoke dilution. Cigarette holders popular in the 1930s provided ventilation. Ventilation is achieved today with small holes around the filter. The primary means of toxin reduction however is the addition of a filter component on the mouth end of the cigarette to trap certain components before they are released from the cigarette in the form of smoke.

The majority of cigarettes sold in the United States today have cellulose acetate filters. Most cellulose acetate filters reduce tar and nicotine yields by 40–50% compared to nonfiltered cigarettes (Neilson and Davis, 1999). Because filter materials influence tar and nicotine smoke yields as well as taste to differing degrees, filter preference has become regionalized. Filters that contain charcoal provide selective removal of a range of vapor-phase smoke constituents and are more popular in Japan than in the United States. Although Japanese and American smokers, smoke a comparable numbers of cigarettes per day there is a lower incidence of lung cancer in Japan (NIH, 1996). Many factors play a role in the differences in cancer rates between countries. It is speculated that along with diet, genetics, epidemic patterns, and other life-style factors, charcoal filters and tobacco processing may contribute as well (Hoffmann and Hoffmann, 1997).

Traditional cellulose acetate filters treated with certain plasticizers can reduce some additional volatile and semivolatile compounds in smoke. The addition of charcoal particles in the filters reduces volatile smoke constituents such as ciliotoxic hydrogen cyanide, acetaldehyde, and acrolein. It can also reduce some volatile aromatic hydrocarbons, such as benzene and toluene, in the first puffs of a cigarette but becomes less effective in later puffs (NIH, 1996). Segmented filter systems, like charcoal-containing filters, provide a multitude of options. Charcoal, for instance, is available in a variety of activities depending on its surface area and pore volume. The amounts of material used in filters, filter length, and particulate removal efficiency can be adjusted (Davis and Nielsen, 1999).

Since about 1968, many filter tips have been perforated with one or more lines of ventilation holes placed around the middle of the filter. Ventilation holes act slightly differently than the permeability ventilation provided by the cigarette paper. Filter tip ventilation is engineered to dilute the smoke as it travels through the cigarette and the filter. The result is an overall reduction in smoke and tar yields at standard smoking conditions to levels that filters, permeable papers or processed tobaccos alone could not achieve. Approximately 80% of U.S. cigarettes have tar yields of 15 mg or less (FTC, 2000); most of these cigarettes have filter tip ventilations (Davis and Nielsen, 1999). The ventilation holes are inserted where smokers are likely to place their fingers or lips, which inhibits the intended use of the vents. Machine-generated smoke yield tests, however, position cigarettes so that the ventilation holes are exposed. Jenkins and colleagues conducted a study in 1982 comparing smoke yields between open and blocked tip ventilation. Their abbreviated results can be found in Table 4-1. The results showed that blocking the ventilated filters (VF) increased the tar, nicotine, and carbon monoxide to levels similar to that of regular filter cigarettes (F).

There have been a few notable historic developments regarding novel cigarette filters of unproven efficacy. The Kent cigarette line produced cigarettes with a novel filter of coiled crepe paper with cotton fibers and crocidolite fibers in the 1950s. Crocidolite is a form of asbestos with fibers so thin that they could be arranged and used to trap particles as small as 1 μ (Longo et al. 1995). The so-called Micronite filter eliminated nearly twice as much tar and nicotine delivered to the smoker as any other standard brand of its time. Yet it failed in the marketplace due to the flavorless smoke and difficulty in drawing on it (Kluger, 1997).

Ligget tobacco company experimented with adding palladium and magnesium nitrate to tobacco in efforts to decrease cancer rates in smokers. Preliminary tests on mice resulted in a 95% reduction in tumors compared to other brands (AP article 1988). Little else known about this innovation, because research ended, reportedly due to litigation, in 1988 (Was a safer cigarette research snuffed, 1994).

A new filter treatment called the "Wellstone Filter" has been developed. The cellulose acetate filter has been treated with a nonbiological compound that supposedly removes nearly 90% of tar and carcinogenic compounds while maintaining taste (Fisher, 2000). Patents are still pending.

Table 4-1 Effect of Smoking Conditions (Blocked Tip Ventilation) on Smoke Yield (mg per Cigarette ± one standard deviation)

Brand	**FTC** (35 ml, 2 sec 1 puff per minute)	**FTC+** **(tip taped** 35 ml, 2 sec, 1 puff per minute)
Tar Yield		
VF-A	3.8±0.5	9.4±0.9
VF-C	2.9±0.6	7.6±0.9
VF-D	1.6±0.2	9.7±0.8
F-A	18.5±1.2	ND
F-C	16.4±1.4	13.2±0.6
F-D	9.9±0.8	11.7±1.3
NF-A	22.5±1.0	21.3±1.5
NF-C	19.4±1.1	21.3±1.0
Nicotine Yield		
VF-A	0.40±0.05	0.72±0.05
VF-C	0.25±0.04	0.45±0.03
VF-D	0.19±0.05	0.62±0.07
F-A	1.09±0.07	ND
F-C	0.94±0.02	0.71±0.06
F-D	0.61±0.02	0.68±0.10
NF-A	1.14±0.05	1.37±0.07
NF-C	1.13±0.13	1.6±0.23
Carbon Monoxide Yield		
VF-A	4.1±0.7	12.3±1.5
VF-C	2.1±0.2	8.7±1.2
VF-D	1.0±0.1	10.7±0.4
F-A	15.7±1.8	ND
F-C	13.4±1.2	17.9±1.2
F-D	8.5±0.3	11.5±0.7
NF-A	11.3±1.0	12.8±2.7
NF-C	11.3±1.2	12.9±0.8

Note: F = filter; ND = not determined; NF = nonfilter; VF = ventilated filter; A,C,D = different brands

Source: Modified from Jenkins and Colleagues, 1982 in NIH, 1996.

R.J. Reynolds also experimented with its own variation on filters. Reynolds created an extra corrugated carbon paper filter for the Winston Select EW brand. It was intended to reduce compounds linked to heart problems. The product was test marketed in Oklahoma City in 1996 (Feder, 1996). (This filter was known more commonly as the "carbon scrubber filter" to reduce free radicals linked to cardiovascular disease.)

Other product modifications of interest for historical reasons include the Favor Smokeless Cigarette and Masterpiece Tobacs. The Favor Smokeless Cigarette was introduced in 1985 and was evaluated soon afterwards by the Food and Drug Administration (FDA), which determined the product to actually be a type of drug delivery device also known as a nicotine inhaler. The FDA removed it from the market. Masterpiece Tobacs is a chewing gum containing shreds of tobacco. Pinkerton Tobacco Company introduced it in 1987. This too was withdrawn from the market when the FDA determined the gum to be a food product with an unapproved food additive, tobacco (Fielding et al.,1998).

Philip Morris also experimented with a modified cigarette with denicotinized tobacco called NEXT. NEXT had a tar yield of 9.3 mg but a nicotine yield of only 0.08 mg. Lacking the addictive component, this product was not successful on the market (Ferrence et al., 2000).

Currently Available and Novel PREPs

Modifications of Conventional Tobacco Products (See table 4-2)

A new curing process is being used for the production of tobacco with substantially reduced tobacco-specific nitrosamines (Star Scientific, 1999). The StarCure™ technology of Star Scientific (formally called Star Tobacco and Pharmaceutical Co.) has a modified and controlled curing process that has used microwaves to kill the bacteria that convert nitrogen-containing compounds into TSNAs. Star has recently stopped using this method and now uses curing barns that decrease microbial activity (Blackwell, 2000). Star Scientific has been using Virginia flue-cured Kentucky burley tobacco in its process. Star expected to bring to market products with only StarCure tobacco in late-2000. Other tobacco companies are reportedly working on methods for reducing or eliminating TSNAs from tobacco (Fairclough, 2000). Brown and Williamson purchased 2 million pounds of low-nitrosamine tobacco from Star in 1999 and contracted for millions of additional pounds in 2000 (Fairclough, 2000; Star Scientific, 2000). Nitrosamines are still formed from these tobaccos upon combustion, but the noncombusted product contains very little or no TSNAs.

Star Scientific has used this modified tobacco along with activated charcoal filters in a new line of cigarettes called Advance™. Star hopes that by replacing traditional filters with the activated charcoal filter, it will reduce the levels of vapor-phase toxins (Star Scientific, 2000; Fairclough, 2000). Star Scientific gives smoking yields on its Web site and claims to have substantially lower TSNA, CO, and tar levels and similar nicotine levels compared to the average of three leading light brands (Star Scientific, 2000). A package insert for Advance™ cigarettes lists these findings as reported independently by the FTC and the Massachusetts Department of Public Health.

Smokeless Tobacco Products

Currently, most smokeless tobacco users in the United States use moist snuff. The 1999 National Household Survey on Drug Abuse reported that among the 66.8 million Americans who

report current use of tobacco products, 3.4% use smokeless tobacco (SAMHSA, 2000). The highest prevalence of smokeless tobacco use was found in males between 18 and 25 years of age (SAMHSA, 2000). The manufacturing of fine-cut tobacco for the production of moist snuff increased in the 1970s. An active advertising campaign is thought to have led to increased prevalence of smokeless tobacco among 18–24-year-old males. From 1970 to 1991, the use of smokeless tobacco in this population increased from 2.2% to 8.9% (U.S. DHHS 2000). For most of the 1990s, the Centers for Disease Control and Prevention's (CDC's) Youth Risk Behavior Survey has shown a consistent use of smokeless tobacco among male high school students at about 20% (U.S. DHHS 2000).

Sweden has a high prevalence rate of smokeless tobacco use: 18% of Swedish men and just under 2% of women aged 15–75 dipped snuff in 1995, compared to 3.3% of American adults (less than 1% of American smokers were women) (Ahlborn, 1997; SAMHSA, 1996). In 1996, only 18% of Swedish adults were daily smokers (primary reference L. Ramstrom, personal communication – from Jimenez-Ruiz 98), whereas in the United States in 1998 the smoking prevalence was 24.1% of adults (18 years and older) (CDC, 2000). In fact, Sweden has the largest per capita consumption of moist snuff. In 1990, Swedish citizens consumed 0.68 kg per person per year, or 4,846 tons annually (Ahlborn, 1997). Swedish snuff differs from snuff in the United States in that it has been shown to contain fewer TSNAs. The difference in recent years has become smaller due to a decrease in TSNAs in U.S. products (Ahlborn, 1997). For the health effects and toxicity of smokeless tobacco, see Chapter 10 of this report. There is debate in the tobacco control field whether smokeless tobacco has a role as a PREP and whether controlling factors such as marketing will prevent its use as a "gateway" to cigarette use.

Cigarette-like Products

Aside from modifications of traditional tobacco products, there has been a recent introduction of cigarette-like products. R.J. Reynolds (RJR) was the first of the tobacco companies to develop such a PREP in 1988, called Premier™.

An RJR monograph about the development of Premier™ describes the prototype product as "similar to other cigarettes in that it requires tobacco for taste and enjoyment" (R.J. Reynolds Tobacco Company, 1988). Premier™ is a cigarette-like product that delivers nicotine with less combustion. This controlled burning reportedly releases volatile, flavorful components, but does not decompose the tobacco. Similar to traditional cigarettes, the smoker inhales an aerosol. The four components of Premier™ include tobacco and tobacco flavor beads, a volatile liquid to form the aerosol or smoke, a heat source to warm tobacco and vaporize the liquid, and finally a system that condenses the vapor into an aerosol delivered to the user (R.J. Reynolds, 1988).

The RJR monograph of this cigarette prototype details the "tar," nicotine, and CO levels using a modified FTC rating. The rating is modified to a version that is not based on the butt length. The prototype ranked lower in tar and nicotine levels compared to all the traditional cigarettes to which it was compared: tar = 6 mg per cigarette (nicotine-free dry particulate matter); nicotine = 0.3 mg per cigarette; CO = 12 mg per cigarette.

This prototype has developed into a new product Eclipse™, which is being sold over-the-counter in Dallas, TX and other test markets and over the telephone and Internet. Eclipse™ has recently been marketed as "a better way to smoke. A Cigarette that responds to concerns about certain smoking-related illnesses. Including Cancer" (R.J. Reynolds Tobacco Company, 2000).

The advertisements for Eclipse™ also address social acceptance because it produces no ash and substantially less visible environmental tobacco smoke (ETS).

Eclipse™ resembles an ordinary cigarette in shape and size just as Premier™ did. The carbon tip is ignited and heats the mixture of tobacco and glycerin before passing through a charcoal filter. The heating unit consists of a carbon fuel element surrounded by a fiberglass insulator. Glycerin contributes to 50–60% of the composition of the light reconstituted tobacco filling of the product. Research has shown that the glycerin has been treated to prevent it from sweating out of the tobacco blend, yet little else is known regarding what additives have been used or how else the tobacco may have been treated. Eclipse™ is different from Premier in that it does not have flavor beads or an aluminum cylinder or the alumna beads (Slade, 1996; Ferrence et al., 2000). These changes are likely to enhance the smoke aerosol so that it more closely resembles that of traditional cigarette products. Tests conducted under FTC-like conditions resulted in 3.2 mg tar, 0.18 mg nicotine, and 7.5 mg CO (R.J. Reynolds Eclipse™ web site, 2000).

In a study conducted by Fagerstrom et al. (2000) measuring nicotine and CO exposure using Eclipse™, nicotine oral inhaler, and traditional cigarettes, it was discovered that there is little difference in nicotine blood concentrations in subjects smoking only Eclipse™ or their usual brand of cigarettes. Eclipse™, however, did produce increased carbon monoxide levels. A recent study commissioned by the Massachusetts Department of Public Health compared Eclipse™ to two conventional low-yield products. Eclipse™ produced higher yields of tar and CO than the comparison products. Under more intensive conditions, the Eclipse™ yields of nicotine were also higher than comparison products, as were specific toxicants, BaP, acroline, and NNK (Labstat, 2000). A scientific panel convened by RJR has also studied the toxicity of Eclipse™ compared to a reference cigarette. Among its many conclusions, this panel reported elevated acrolein, furfural, formaldehyde, and CO in the smoke from Eclipse™ when compared to a ultra-low tar reference cigarette (Eclipse™ Expert Panel, 2000). The panel went on to report a significant reduction in evidence of lower respiratory tract inflammation and tumorigenic activity in dermal studies.

Philip Morris Tobacco Company has developed and marketed a PREP with some similarities to Eclipse™. It differs significantly in other ways. Preliminary technical information on Accord™ was publicly presented by Philip Morris scientists in a poster presentation at the Society of Toxicology in 1998. They began consumer testing in the fall of 1997 (Jones, 1998). Like Eclipse™, Accord™ uses the lower temperature and controlled burn of the cigarette to dramatically alter the composition of smoke produced. Accord™ burns at 950 °F, or 700 °F lower than the traditional cigarette. The burning device in the Accord™ cigarette is powered by rechargeable batteries in a beeper-sized unit called a Puff Activated Lighter (Holzman, 1999). This unit fits special Accord™ cigarettes and powers a microchip that senses when the cigarettes are being drawn on. When signaled, it produces a controlled 2-second burn from one of eight heating blades around the cigarette and thus delivers smoke to the user.

The company reports that Accord™ delivers 3 mg of tar and 0.2 mg of nicotine, similar to other Philip Morris ultralight products (Jones, 1998). Philip Morris scientists report that Accord™ smoke contains marked reductions in 35 of 53 potentially hazardous compounds and that Accord™ produces 83–98% less carbon monoxide, benzene, and nitrogen-based compounds than the cigarette smoke of comparison products (Jones, 1998). The data was stated without specifying the nature of the comparison products. Like Eclipse™, Accord™ does not produce ash and produces little ETS (ASH, 1997). A recent study indicates that smokers who switch to

Accord™ under experimental conditions are exposed to minimal CO and less nicotine compared to their usual brand (Buchhalter and Eissenberg, 2000).

Table 4-2 Tobacco Products

Product	Company	Year	Key Characteristics
Kent	B&W	1950s	Micronite filters
Spectra	Kinney	1980's	Contained N bloctin, designed to block nitrosamine absorption in the lungs
Favor Smokeless Cigarette		1985	Nicotine inhaler
Premier	R.J. Reynolds	1987	Less combustion than conventional cigarette
Masterpiece Tobacs	Pinkerton	1987	Chewing gum with tobacco shreds
NEXT	Philip Morris	1989	Low-nicotine cigarette
Eclipse™	R.J. Reynolds	1996	Less combustion than conventional cigarette
Winston Select	R.J. Reynolds	1996	Extra corrugated carbon paper filter
Accord™	Philip Morris	1998	Lower operating temperature than conventional cigarette and heat produced from electrical resistance
Advance	Star Scientific	2000	Low-nitrosamine cigarette

PHARMACEUTICAL PRODUCTS

Unlike tobacco products, medications developed to aid smoking cessation have undergone rigorous scientific and regulatory examination. Medications for the treatment of tobacco dependence came into existence in the 1970s in Europe and 1980s in the United States. The first effective medications for the treatment of nicotine dependence were nicotine replacement therapies. Currently, there are four different nicotine replacement products that have been approved by the Food and Drug Administration. These products include nicotine gum, transdermal nicotine. nicotine inhaler, and nicotine nasal spray. The only nonnicotine medication for smoking cessation that is approved by the FDA is bupropion sustained release (SR), or Zyban™. This product. originally marketed as an antidepressant, was initially observed to reduce smoking among depressed patients (Personal communication, Linda Ferry). Subsequent clinical trials among smokers showed that this agent is an effective smoking cessation aid.

In the United States, the FDA has approved these medications only as cigarette smoking cessation aids. Currently, these pharmaceuticals are not recommended solely for the purposes of reducing the number of cigarettes or as a step toward achieving abstinence, to treat withdrawal symptoms or craving in situations when smoking is not allowed, or for quitting tobacco products other than cigarettes. In addition, the safety and efficacy of these medications in pregnant smokers have not been determined, and the use of medications to aid smoking cessation in this population has been delegated to the discretion of the physician.

It is important to note that the pharmaceutical industry was required to provide ancillary behavioral treatments along with the medications to assist the smoker in quitting. These behavioral treatments range from general self-help materials, to tailored self-help materials, to telephone counseling. The FDA imposed this requirement because cigarette smoking not only is considered a physical addiction to nicotine but also is associated with behavioral components. Research results indeed show that behavioral treatment will augment the success rates of medications alone, and the more intensive the treatment is, the greater is the rate of abstinence (Fiore et al., 2000). However, the use of medications with minimal or no behavioral treatments still outperforms placebo treatment, as demonstrated by the efficacy of over-the-counter nicotine medications (Fiore et al., 2000). Therefore, harm reduction approaches with medications may have to be considered in the context of ancillary behavioral treatments.

Nicotine Replacement Products

The concept of the use of nicotine replacements was first fully described by Ferno (1973). The principles behind nicotine replacements are to (1) provide cigarette smokers a sufficient amount of nicotine to allay some of the withdrawal symptoms experienced shortly after tobacco abstinence; (2) to permit progressive reduction of the level of nicotine exposure, leading to eventual ease of totally withdrawing from nicotine products; and (3) to reduce the abuse potential of nicotine due to the slower rate of nicotine absorption. The validity of these principles and mechanisms has been demonstrated by a number of studies (see Henningfield and Keenan, 1993; Hughes, et al., 1989). Other potential mechanisms accounting for product efficacy could be the reinforcing effects derived from nicotine or, on the other hand, blocking the reinforcing effects of nicotine from cigarettes. Chronic exposure to nicotine could result in desensitization of nicotinic cholinergic receptors, thereby blocking potentiation of the nerve. In addition to these beneficial effects, the administration of nicotine medications is associated with significantly lower toxicity than cigarettes since the main ingredient in these replacement products is nicotine with no other toxic elements. The toxicity associated with nicotine alone is confined primarily to reproductive disorders and enhancement of cardiovascular risk factors (Benowitz, 1998), although nicotine's contribution to cardiovascular disorders is minimal compared to that of cigarettes.

Nicotine polacrilex, or nicotine gum (Nicorette™), manufactured by Pharmacia Upjohn, was introduced first in Europe and approved for marketing in the United States in 1984. Nicotine gum was initially a prescription medication in the United States but, in 1996, became an over-the-counter medication. In 1998, a mint-flavored nicotine gum was approved in the United States and it was marketed in 1999. An orange flavored version has recently been introduced. Two doses of nicotine gum are currently available, 2 and 4 mg. In 1991 and 1992, the United States was introduced to nicotine patches distributed by four different pharmaceutical companies. The first patch introduced in the U.S. market was Habitrol™ (marketed and manufactured by Ciba-Geigy, and now by Novartis); then Nicoderm™ (manufactured by Alza Corporation, marketed by Marion Merrell Dow, then Hoescht Marion Rousel, followed by SmithKline Beecham, now GlaxoSmithKline); Nicotrol™ (manufactured and marketed by Pharmacia Upjohn); and finally Prostep™ (manufactured by Elan and initially marketed by Lederle as a prescription medication; currently generic patches using a different patch technology are being manufactured by Perrigo). Nicotine patches were initially prescription only, but both Nicoderm CQ™ and Nicotrol™ were approved to go over the counter in 1996. Habitrol™ and a modified Prostep™ are now sold as generic products through major drugstore chains. Nicotine patches are available in three different doses for Habitrol™ and Nicoderm CQ™ (21, 14, and 7 mg). Nicotrol™ was available in three

different doses (15, 10, and 5 mg) by prescription, but only in one dose (15 mg) over the counter. Perrigo's patches are available in 22-mg and 11-mg doses. The nicotine inhaler was introduced on the market in 1998 and is regulated as a prescription drug. This product is a tube-shaped device that contains a porous plug saturated with nicotine enclosed in a replaceable plastic cartridge. The nicotine inhaler is puffed upon like a cigarette, but absorption occurs primarily buccally and from the upper airway and not in the lungs because its design does not provide an aerosol that could be substantially inhaled in the lung. Each cartridge contains 10 mg of nicotine, with 13 μg delivered with each puff (compared to 100 μg delivered with cigarettes), which is about one-tenth the nicotine dose from puffing on a cigarette. The nicotine nasal spray was introduced to the U.S. market around 1997 and is also regulated as a prescription drug. The dosing for nicotine nasal spray is one spray in each nostril, delivering 0.5 mg of nicotine per spray for a total dose of 1 mg.

Each product has a different route of administration, instructions for use, amount of nicotine absorbed, and speed of nicotine delivery. Nicotine patches are used once a day, with a patch being placed on the skin in the morning and taken off prior to bedtime or the next morning. For nicotine gum, a fixed schedule of use (e.g., at least one piece every 1–2 hours, with a maximum of 24 pieces per day) is recommended to achieve sufficient levels of nicotine. The nicotine inhaler is puffed on, not inhaled like a cigarette, and used ad libitum. The recommended number of cartridges is 6–16, with each cartridge used in 3 smoking periods. For the nicotine nasal spray, the recommended initial dosing is 1–2 sprays per hour, with a minimum recommended treatment of 8 doses per day and a maximum of 40 doses per day. The recommended duration of treatment for all these products ranges from 3 to 6 months.

The route of administration will contribute to the side-effect profile and contraindications (see Table 4-3). Contraindications include smokers in the immediate postmyocardial infarction period, with serious arrhythmias and with serious or worsening angina pectoris. Studies in individuals with stable cardiovascular disease have shown that smokers who used nicotine patches were not at greater risk for cardiovascular events than those assigned a placebo (Joseph et al., 1996), even when used while smoking a cigarette (Working Group for the Study of Transdermal Nicotine in Patients with Coronary Artery Disease, 1994). For pregnant or lactating female smokers, nicotine replacements are recommended only when the use of psychosocial treatment has failed and the benefits of abstinence achieved from using the nicotine replacements outweigh the risk of nicotine replacement and potential concomitant smoking (Fiore et al., 2000). In general, the contraindications and side effects are minimal with these products.

Table 4-3 Side Effects and Contraindications of Nicotine Replacement Products

Product	**Most Frequent Side Effects**	**Contraindications**
Nicotine gum	Jaw ache, mouth soreness, dyspepsia, hiccups	TMD, Dentures
Nicotine inhaler	Local irritation of mouth and throat, coughing, rhinitis	Allergy to menthol
Nicotine patch	Local skin reaction, sleep disruption	Skin disorders
Nicotine spray	Nasal and airway irritation	Reactive airway disease, sinusitis
Bupropion	Insomnia and dry mouth	Seizures, concurrent use of

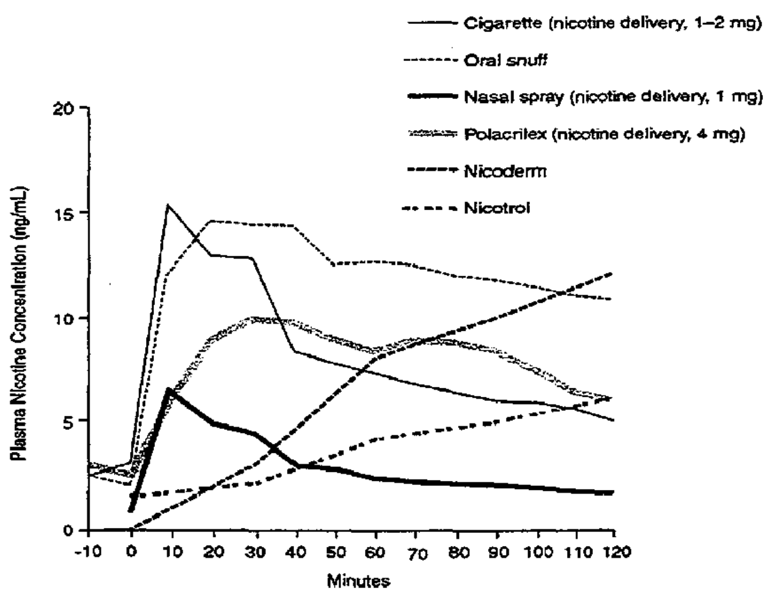
		MAO inhibitors, history of eating disorders

NOTE: MAO = Monoamine Oxidose; TMD = J temporomandibulor joint disfunction.

SOURCE: Information gathered from Fiore et al., 2000.

The bioavailability (see Table 4-4) and amount of nicotine absorbed per unit dose (see Figure 4-1) varies across products. The mean nicotine peak concentrations attained from tobacco products are higher than those of all nicotine replacement products. Furthermore, for cigarettes, high arterial plasma nicotine concentrations are achieved that are not reached by nicotine replacement products (Henningfield et al. 1993). The daily dose of nicotine from medications used ad libitum will depend on the frequency of use. Typically, these products are underutilized in terms of both frequency and duration. Rarely does the daily level of nicotine concentration attained by the use of these products exceed three-fourths the level attained with cigarettes and typically ranges from one-fourth to two-thirds of the cigarette level (Benowitz et al. 1988; Hjalmarson et al. 1997; Leischow et al., 1996; Schneider et al. 1995; Schneider et al. 1996; Sutherland et al. 1992; Tonnesen, et al. 1993).

Figure 4-1 Venous blood concentrations



NOTE: Venous blood concentrations in nanograms of nicotine per millimeter of blood as a function of time for various nicotine delivery systems.

SOURCE: Reprinted with permission from Fant, RV, Owen, LL, Henningfield, JE. Nicotine Replacement Therapy. Primary Care 26(3); 1999.

Table 4-4 Bioavailability of Nicotine

Product	**Bioavailability per Dose**
Cigarette	1–2 mg
Smokeless tobacco	3.6–4.5 mg
Nicotine gum (2 or 4 mg)	1 or 2 mg
Nicotine inhaler	2 mg per cartridge
Nicotine patch	15–22 mg (over 16–24 hr)
Nicotine spray	0.5 mg

Source: Data from Benowitz, 1988; Fagerstrom, 20000; Fant, et al. 1999.

The time to reach peak blood nicotine concentrations (T_{max}) also varies across products. The nicotine replacement product that has the shortest T_{max} is nicotine nasal spray followed by nicotine inhaler, nicotine gum, and finally the nicotine patch (see Figure 4-1 and Table 4-5). It should be noted that a faster T_{max} for nicotine nasal spray was observed with arterial than with venous blood (mean value, 5 vs. 25 minutes, respectively) as well as a higher maximum nicotine concentration (mean value, 10 vs. 5 ng/ml; Gourlay and Benowitz, 1995).

Table 4-5 Pharmacokinetics

Product	**Time to Maximum (T_{max}) for Venous Blood**
Cigarettes	Within 5 min.
Smokeless tobacco	20–30 min.
Nicotine nasal spray	10 min.
Nicotine gum (2-4 mg)	30 min.
Nicotine inhaler	20–30 min.
Nicotine patch	4–9 hr.

SOURCE: PDR, 2000; Benowitz et al. 1988.

The faster the speed of nicotine delivery, rate ~~of absorption~~, and attainment of peak level, the greater is the likelihood of continued use ~~or abuse~~ (deWit and Zacny, 1995). The fastest time for maximum nicotine concentration occurs with cigarettes, followed by nicotine nasal spray, smokeless tobacco, then other nicotine replacement agents. Smokeless tobacco appears to take longer or seems equal in time to reach maximum concentrations compared to some nicotine replacement products such as nicotine gum and inhaler. However, the abuse potential is likely to be greater for smokeless tobacco not only because of the amount of nicotine delivered, but also

because a nicotine boost of 10 ng/ml has been observed within the first 10 minutes of use (Holm et al., 1992). This venous level is higher than the maximum venous concentration observed with other nicotine products including from nicotine nasal spray.

Although few studies have examined the abuse potential across various nicotine replacement products, it remains significantly lower than that of cigarettes. Of the few nicotine replacements studied, withdrawal symptoms and the rate of use beyond the recommended period for the nicotine patch appear to be minimal and the abuse potential appears to be low (see deWit and Zacny, 1995; Hughes, 1998). In clinical trials, prolonged use of nicotine gum (e.g., 12 months) is around 22% among abstinent smokers, but about 9% of those who have been randomly assigned to the gum (Hughes, 1998). Similar rates of prolonged use are observed for nicotine inhaler (Schneider et al., 1996; Tonnesen et al., 1993). For nicotine nasal spray, about 29–43% of individuals who have quit smoking reported use of the active spray at 12 months compared to 0% in the placebo spray group, even though the recommended period of use was 3 months (Hjalmarson et al., 1994; Sutherland et al., 1992). Of smokers assigned to the active nasal spray, about 10% continued to use it at 12 months (Hjalmarson et al., 1994). This finding would indicate that continued use of this product might be greater than that of other nicotine products. It is important to note that the continued use of nicotine products may be motivated by the desire not to relapse to smoking rather than addiction to the product. Furthermore, the cost of the product plays a role in continued use as well, with higher cost deterring longer use. All of the aforementioned studies provided the nicotine products for free, and therefore the rate of continued use may be highly exaggerated. In a nonresearch setting, the unit dose costs of cigarettes and smokeless tobacco are typically less than or equivalent to those of the medication (see Table 4-6). However, medications must be bought in larger quantities, resulting in yet higher costs per purchase.

Table 4-6 Costs for Tobacco Products and FDA-Approved Medications[a]

Product	Cost per Day
Cigarettes (20 per day)	$1.70–$4.85 per pack
Smokeless tobacco[b]	$1.88–$2.00
Nicotine gum	$4.26–$6.87 (10 2–4 mg pieces)
Nicotine inhaler	$10.81–$10.94 for 10 cartridges
Nicotine patch	$2.36–$4.50
Nicotine spray	$4.50–$9.20 for 10–20 doses
Bupropion	$3.33–$3.40

[a]Prices are from U.S. PHS guidelines and based on the retail price of the medication purchased at a national chain pharmacy located in Madison, Wisconsin, and Minneapolis, Minnesota.

[b]Cost per day is based on a mean use of 3.5 tins per week (Hatsukami and Severson, 1999) at $3.75 to $4.00 per tin.

Based on a report issued by the Public Health Services (Fiore et al., 2000), the nicotine replacement products have comparable rates of treatment success. The PHS undertook an extensive meta-analysis of studies to determine the efficacy of various medications for smoking cessation. Only published, peer-reviewed and randomized controlled studies with a follow-up time of at least 5 months post-quit were included in the analyses. The primary outcome variable was point prevalence abstinence (not smoking in the past week), unless only data for continuous abstinence (or of an unknown nature) were available. Data for the efficacy of various medications are presented in Table 4-7. The estimated odds ratios range from 1.5 to 2.7 for active nicotine

replacements VS. the controls and the estimated rates of abstinence range from 18 to 31% for active nicotine replacements VS. 10 to 17% for the controls. Several trials have been conducted with nicotine patches that simulate over-the-counter use. The estimated rates of abstinence observed in these studies are about 11.8% with active nicotine patch and 6.7% with placebo patch with an estimated odds ratio (OR) of 1.8 (Fiore et al., 2000).

Table 4-7 Efficacy of Nicotine Replacement Products

Medication	Abstinence Rate: Active (95% C.I.)	Abstinence Rate: Placebo	Odds Ratio (95% C.I.) PHS (Cochrane)
Gum (N = 13 studies)	24 (21, 27)	17	1.5 (1.3, 1.8) (1.6 [1.5, 1.8][a])
Inhaler (N = 4 studies)	23 (16, 29)	11	2.5 (1.7, 3.6) (2.1 [1.4, 3.0][b])
Nasal spray (N = 3 studies)	31 (22, 39)	14	2.7 (1.8, 4.1) (2.3 [1.6, 3.2][c])
Patch (N = 27 studies)	18 (16, 20)	10	1.9 (1.7, 2.2) (1.8 [1.6, 1.9][d])

NOTE: CI = Confidence Interval.

[a]N = 48 studies

[b]N = 4 studies

[c]N = 4 studies

[d]N = 31 studies

SOURCE: Abstracted from Fiore et al., 2000; Lancaster et al., 2000.

Similar meta-analyses have been conducted by the Cochrane Tobacco Addiction Group (Lancaster et al., 2000). Randomized controlled trials (published and unpublished) with at least 6 months' follow-up were included in the analyses. Sustained abstinence was the primary outcome examined, rather than point prevalence, although point prevalence rates were used when sustained abstinence rates were unavailable. The results are very similar to PHS results. The odds ratio across the nicotine products ranged from 1.7 to 2.3 for active nicotine replacement VS. control, and efficacy was similar across products (see Table 4-7).

Other Nicotine Replacement Agents and Nonapproved Methods of Use

Several other nicotine replacement products have been tested, but are not currently on the market. These products include a sublingual nicotine tablet (Molander et al., 2000), the oral nicotine transmucosal (Leischow et al., 1996); and the nicotine lozenge (Foulds et al., 1998). Other nicotine replacement products are likely to be developed in the future. It is likely that

nicotine replacements with a faster speed of delivery that mimic the effects of cigarettes will be explored, with the hopes that such delivery devices would be safer than nicotine-containing tobacco products. In addition, fast nicotine delivery devices may lead to greater treatment success or provide a bridge toward using slower nicotine absorption products. Future replacement medications are also likely to become more sophisticated, targeting specific nicotinic receptor subtypes that are associated with specific functions.

Many researchers also believe that combinations of different types of nicotine replacements might be more effective than single agents alone (Fiore et al., 2000). Combination products would result in higher levels of nicotine replacement, which may lead to less desire to smoke and less reinforcement from a cigarette when smoked due to the development of tolerance. Interestingly, doses greater than 21 mg of nicotine generally show minimal increases in long-term abstinence rates (Hughes et al., 1999), although the Cochrane Group found that high-dose nicotine patches were marginally more effective than a standard dose (1.2, 95% CI=1.0 to 1.4; $N = 6$ trials). However, combinations of nicotine patch with nicotine products that can be used ad libitum have resulted in better treatment success. The use of the nicotine patch would result in a steady-state trough level of nicotine to prevent withdrawal symptoms, whereas the ad libitum product could be used during periods when an urge to smoke is experienced. Treatment studies have been conducted that examine a combination of nicotine gum and patch (Kornitzer et al., 1995; Puska et al., 1995); nicotine spray and patch (Blondal et al, 1999); and nicotine inhaler and patch (Westman et al., 2000). Results from the meta-analyses conducted with some of these studies showed that a combination treatment approach was more effective than a single treatment approach (OR = 1.9, 28.6% vs. 17.4%, respectively (Fiore et al., 2000). Furthermore, two studies showed that a combination approach led to greater reductions in withdrawal symptoms compared to a single treatment approach (Fagerström, 1994; Fagerström et al., 1993).

Antidepressants

To date, the antidepressants that have been successful in treating smokers are bupropion SR and nortriptyline. Bupropion SR, or Zyban™, which is approved by the FDA, is recommended as a first-line pharmacotherapy similar to other nicotine replacement therapies (Fiore et al., 2000). Nortriptyline, which is not approved for this indication by the FDA, is recommended as a second-line treatment for smokers who were unresponsive to the first-line treatment. The mechanism of action of various antidepressants is unknown. Understanding these mechanisms is important in order to refine and develop drugs that are targeted to specific population of smokers or essential neurotransmitter systems. As one mechanism, it is possible that since a higher incidence of depression is observed among smokers than nonsmokers (Breslau et al., 1991; Glassman et al., 1990; Kendler et al., 1993) and smokers with a history of depression are more likely to relapse (e.g., Anda et al., 1990; Covey et al., 1990; Glassman et al., 1990; Hall et al., 1993) and experience depressive symptoms or mood after cessation (Borrelli et al, 1996; Glassman et al., 1990), antidepressants may be effective in enhancing treatment efficacy among this population. However, clinical studies show that antidepressants are effective for smoking cessation in both non-depressed and depressed populations (Fiore et al., 2000). Another mechanism is the use of antidepressants to reduce withdrawal symptoms. Tobacco withdrawal symptoms overlap with symptoms associated with major depression—depressed mood, irritability, low energy, and problems with sleep. A third possible mechanism may be that antidepressants and nicotine release similar neurotransmitters. For example, since bupropion is a weak dopamine uptake inhibitor (Ascher et al., 1995), the efficacy of this product has been attributed to an increase in do-

pamine levels. Dopamine levels are increased by nicotine and constituents in tobacco smoke, and this increase is thought to be responsible for some of the positive reinforcing effects of cigarette smoking. Bupropion also weakly blocks the neuronal reuptake of noradrenaline (Ascher et al., 1995; Ferris and Cooper, 1993; Perumal et al., 1986), and increased noradrenaline levels may also serve a reinforcing function. Nortriptyline is a tricyclic antidepressant drug that is also known to enhance levels of noradrenaline and to have some serotonergic activity. Interestingly, both medications also decrease firing of the locus ceruleus. The beneficial effects from inhibiting firing in the locus ceruleus may be derived from blocking the pathways of acute nicotine stimulation or resembling the desensitized state seen with continuous nicotine exposure (Benowitz and Peng, 2000). Finally, a preliminary study suggests that bupropion may act as a noncompetitive antagonist of nicotinic acetylcholine receptors, an action that is independent of its antidepressant mechanisms of action (Fryar and Lucas, 1999).

Fluoxetine and sertraline target primarily the serotonin system and are serotonin reuptake inhibitors. Antidepressants that target the serotonin system do not show enhanced efficacy over placebo, although some preliminary evidence exists that fluoxetine may be effective as a smoking cessation aid in smokers experiencing symptoms of depression at baseline (Niaura et al., 1995). In a very small trial, doxepin, a tricyclic antidepressant, reduced the number of cigarettes smoked and increased short-term success compared to placebo (Edwards et al., 1998), but no larger clinical trials with long-term follow-up have been conducted at this time. Other antidepressants, such as moclobemide, a monoamine oxidase (MAO) inhibitor, have shown equivocal success (Berlin et al., 1995).

Bupropion was approved as a prescription medication for smoking cessation in 1997. At a constant daily dose, it takes about 8 days for bupropion blood levels to reach steady state. There is an active metabolite that takes even longer to reach steady state. Consequently, the dosing procedure involves taking bupropion 1–2 weeks prior to the quit date. Smokers are instructed to take 150 mg per day during the first 3 days and 300 mg per day thereafter for 7–12 weeks. Side effects include primarily dry mouth and insomnia.

In general, dose-related effects are observed with bupropion. At 1 year, point prevalence smoking cessation rates are significantly different between placebo and 150 or 300-mg bupropion per day, but not between placebo and 100 mg per day (Hurt et al., 1997). For the 150-mg and 300-mg doses, the OR was approximately 2.0, with abstinence rates of around 23% at 12-month follow-up versus 12% with placebo (Hurt et al., 1997). Continuous abstinence rates (biochemically confirmed not smoking at each visit) were highest among the 300-mg (24.4%) and 150-mg (18.3%) groups versus placebo (10.5%). In another study, bupropion and bupropion plus nicotine patch were observed to be more effective than placebo or nicotine patch alone, although in this study the efficacy of the patch was unusually poor (Jorenby et al., 1999). Based on the PHS meta-analyses of these two studies, the OR was 2.1 (95% C.I.=1.5, 3.0) for bupropion compared to placebo, and the estimated abstinence rate was 30.5% versus 17.3% (Fiore et al., 2000). The Cochrane review (Lancaster et al., 2000) also found a similar OR of 2.7 (95% C.I.=1.90, 3.9) based on the two published studies and 2 unpublished smaller studies. The efficacy of bupropion is unrelated to a history of major depression (Hayford et al., 1999).

Nortriptyline also involves a dosing procedure that is initiated 10–28 days prior to quitting to achieve steady-state levels. Dose initiation begins at 25 mg per day and escalates to 75–100 mg per day. The duration of treatment in published trials has been about 12 weeks. Two studies have shown that nortriptyline is more effective than placebo (Hall et al., 1998; Prochazka et al., 1998) with an OR of 3.2 (95% C.I.=1.8, 5.7) for nortriptyline compared to placebo and estimated absti-

nence rates of 30.1% and 11.7% respectively, (Fiore et al., 2000). These results were similar to those observed in the Cochrane review (OR 2.8, 95% CI=1.6, 5.0; Lancaster et al., 2000). This rate of success again is independent of a history of depression. Although this medication costs less than bupropion, there is concern about side effects, particularly overdose. Side effects include sedation, dry mouth, blurred vision, urinary retention, lightheadedness, and shaky hands.

Other Medications

Antagonists — withdrawal

Other medications to aid cessation have an antagonist effect, that is, they prevent the drug from acting on the receptor site. This antagonist action would reduce the reinforcing effects from smoking and thereby decrease some of the satisfying aspects of smoking and the desire to smoke. Mecamylamine is a nonspecific nicotinic receptor antagonist that was originally used as an antihypertensive agent. Mecamylamine has been shown to block many of the physiological, behavioral, and reinforcing effects of nicotine (Collins et al., 1986; Corrigall and Coen, 1989; Levin and Rose, 1991; Martin et al., 1989; Stolerman, 1986). Mecamylamine also decreases craving for cigarettes and reduces nicotine preference (Rose et al., 1989). Clinical trials have focused on the use of a combination of mecamylamine and the nicotine patch. The rationale behind this antagonist–agonist combination is that both mecamylamine and nicotine from the patch would block the reinforcing effects of nicotine by occupying the nicotinic receptor sites. In addition, the nicotine patch would reduce the experience of withdrawal and minimize adverse side effects from the peripheral ganglionic blockade produced by mecamylamine. One of the major problems with the use of mecamylamine is constipation as a side effect, although at lower doses this side effect is not as much of a problem. An early smoking cessation trial with a small sample size showed that a combination of mecamylamine and the nicotine patch demonstrated greater success than the patch alone (Rose et al., 1994). In a later trial, precessation treatment with mecamylamine with or without the nicotine patch compared to no-mecamylamine conditions (nicotine patch alone or no drug) led to significantly higher continuous abstinence throughout treatment in smokers, who later all received both the nicotine patch and mecamylamine after the quit date (Rose et al., 1998). The 6-month continuous abstinence rates were high only in the nicotine–mecamylamine pre-cessation condition compared to pooled data from the other groups. These trials also showed greater reductions in craving, satisfaction from smoking, and smoking rates during the pre-quit period when mecamylamine and the nicotine patch were administered together compared to any drug alone. A subsequent larger clinical trial showed a higher abstinence rate at 7 weeks post-treatment with the combination approach compared to the patch alone, but only in females (Rose et al., 1999).

Another type of antagonist treatment that has been examined only in animal models is immunization to produce nicotine-specific antibodies. Such antibodies would reduce drug entry into the central nervous system by binding to circulating nicotine and thereby decreasing the concentration of unbound nicotine. In animal studies, the nicotine vaccine has been found to reduce nicotine in the brain in a dose-dependent manner (Hieda et al., 1997; Pentel et al., 2000); to block the relief of withdrawal symptoms from nicotine administration in rats undergoing abstinence; and to block behavioral (locomotion), physiological (blood pressure), and neurochemical adrenocorticotropic hormone (ACTH) release effects from nicotine administration (Pentel et al., 2000, and personal communication, 2001). Studies are under way to examine the effects of this vaccine on nicotine self-administration. This approach is an attractive intervention because of its

specificity and lack of direct impact on the central nervous system, although one concern may be attempts to surmount the effects of the vaccine by intensive compensatory smoking.

Nicotine has been shown to release endogenous opioids, which may be responsible for some of the reinforcing effects from smoking (Pomerleau and Pomerleau, 1984; Taylor and Gold, 1990; Watkins et al., 2000). An opioid antagonist may therefore reduce smoking by blocking the endogenous opioid-induced reinforcing effects. The effect of naloxone and naltrexone on smoking behavior has been variable, with some studies showing that naloxone reduces smoking compared to placebo in a laboratory session (Gorelick et al., 1989; Karras and Kane, 1980), while other studies showed no effect of naloxone (Nemeth-Coslett and Griffiths, 1986) or naltrexone (Sutherland et al., 1995) on smoking rate. Naltrexone has been successfully used for the treatment of opioid and alcohol abuse and dependence. Although, earlier studies showed some promise for naltrexone as a smoking cessation aid, long-treatment outcome success has not been enhanced by naltrexone over placebo, even in combination with the nicotine patch (Wong et al., 1999).

Medications That Target Other Systems

Clonidine is another antihypertensive that has been used to promote smoking cessation. Its mechanism of action is likely through stimulation of the α_2 adrenergic autoreceptors in the brain stem, which results in decreased noradrenergic activity and inhibits firing in the locus ceruleus. In a study conducted about 15 years ago, clonidine was observed to alleviate withdrawal symptoms from opiates, alcohol, and cigarettes (Glassman et al., 1984). Because of the observed reductions of nicotine withdrawal symptoms, several clinical trials have been undertaken to determine the effects of clonidine in the treatment of smokers. The PHS performed a meta-analyses on five randomized, placebo-controlled trials with at least 5 months follow-up post-quit (Fiore et al., 2000). This analysis found that clonidine, administered either orally or transdermally, is effective as a smoking cessation aid, resulting in a twofold increase in cessation compared to placebo (estimated abstinence rates of 25.6% vs. 13.9%, respectively; oR=2.1 (95% C.I.=1.4, 3.2). A Cochrane review (Lancaster et al., 2000) of six trials showed evidence of similar efficacy (OR = 1.9, 95% C.I.=1.3, - 2.7). When examining individual studies, some studies showed greater efficacy among women than men (Gourlay and Benowitz, 1995). One study found greater treatment effect in women who are heavily dependent and/or who experience recurrent episodes of depression (Glassman et al., 1993). In another study, more dependent smokers (classified with a Fagerstrom score of $\geq$7) experienced greater efficacy with higher compared to lower concentrations of clonidine, whereas efficacy was independent of clonidine concentrations in smokers with low dependence scores (Niaura et al., 1996). Because of the proven efficacy of clonidine, the PHS has recommended using clonidine as a second-line pharmacological treatment. However, the main drawback to
using clonidine is the profile of side effects, which include dry mouth, drowsiness, dizziness, sedation, and constipation as well as lowering of blood pressure. In addition, rebound hypertension may occur when the medication is discontinued.

Medications other than antidepressants that target the serotonin system, such as buspirone, a partial serotonin (5-hydroxytryptamine) agonist having anxiolytic effects that may also increase firing of dopaminergic and noradrenergic neurons (Benowitz and Peng, 2000), have produced equivocal results with regards to short-term treatment outcome. One study showed positive results with buspirone (West et al., 1991), and two studies showed negative results (Robinson et

al., 1992; Schneider et al., 1996). One other study showed enhanced rates of abstinence at the end of treatment, but not at long-term follow-up, for those individuals with high levels of anxiety but not for those with low anxiety levels (Cincirpini et al., 1995). Effects on withdrawal symptoms have also been equivocal, with some studies showing positive effects of this medication in reducing withdrawal symptoms (Gawin et al., 1989; Hilleman et al., 1992) and other studies showing no effect (Cincirpini et al., 1995; Robinson et al., 1992; Schneider et al., 1996; West et al., 1991).

One innovative proposal for treating cigarette smokers is to change the rate of nicotine metabolism. Nicotine is metabolized primarily by the hepatic CYP2A6 (cytochrome P-450) enzyme. Several studies have examined the effects of having normal homozygous CYP2A6*1 (wild-type) alleles compared to inactive or mutated CYP2A6 alleles on nicotine metabolism and smoking behavior in humans. A prior study with a small sample size showed that smokers homozygous for the CYP2A6 deletion (and therefore having impaired enzyme function) showed lower cumulated urinary cotinine excretion compared to individuals who were homozygous CYP2A6*1 (Kitagawa et al., 1999). In another study, tobacco-dependent smokers who are carriers of null or inactive alleles (CYP2A6*2 or CYP2A6*3), were observed to smoke fewer cigarettes per week than smokers with two active CYP2A6 alleles (Pianezza et al., 1998). Results from both of these studies were duplicated by another study showing that smokers with defective alleles (*4 and *2) smoked fewer cigarettes and demonstrated lower expired CO levels than smokers with homozygous wild-type alleles. Cotinine levels were lower in the group with the defective alleles, and the nicotine–cotinine ratios were higher in this group (Tyndale et al., 2000). One clinical laboratory study examined the effects of methoxsalen, a CYP2A6 inhibitor, on cigarette smoking and found that methoxsalen in combination with oral nicotine decreases carbon monoxide exposure, smoking rate, latency between lighting the first and second cigarettes, and number of puffs taken (Sellars et al., 2000) compared to a placebo–placebo condition. No differences in cigarette consumption or CO exposure were observed with oral nicotine or methoxsalen alone. To date, these results are suggestive of the role of nicotine metabolism in smoking behavior.

Summary and Recommendations:

In summary, many different types of medications have demonstrated efficacy: nicotine replacement therapies, antidepressants, and other medications that target the dopaminergic and noradrenergic systems. These medications have also been shown to be safe and to produce minimal dependence and misuse. New antagonist medications, such as the nicotine vaccine or medications that may alter the metabolism of nicotine, are being evaluated for their effort on smoking cessation. Furthermore, with increasing knowledge of the function of various nicotinic receptor subtypes, medications that target the specific receptor subtypes responsible for the reinforcing effects of nicotine are likely to be developed. Unfortunately, although current smoking cessation aids are effective and relatively safe, the use of these medications by smokers to facilitate cessation attempts is not widespread. New prescription rates represent only 10% share of the approximately 24 million quit attempts made per year (Shiffman et al., 1998), or 15% of the 16 million who attempt to stop smoking cigarettes for at least 24 hours (CDC, 2000). Obstacles to the use of these medications include cost, consumer concern, and misperception regarding the health effects of nicotine and the limitations presented by prescription status (Shiffman et al., 1998).

Medications that are now available over the counter (OTC) have had a significant impact on the number of quit attempts. With the introduction of OTC nicotine patch and nicotine gum, the estimated number of pharmacological quit attempts increased from 2 million to 3 million in 1993–1995 to 6 million in 1996 with numbers increasing in 1997 and remaining stable in 1998 (CDC, 2000). Successful quitting has been estimated to increase by 6%–20% when OTC products are made available compared to when only prescription products are available (Lawrence et al., 1999; Shiffman et al., 1998). If significant reduction in harm is to be achieved, easier access to and reduced costs of these products are necessary.

Another area that requires attention is misinformation regarding the safety of nicotine. In a survey, the majority of smokers (86%) perceived nicotine as harmful (Ketchum and Harris, 1996). Of further concern is the fact that despite the proven efficacy of existing pharmacological agents, relapse rates still remain high at around 60–75%, with even higher rates (exceeding 95%) among those who quit on their own. Furthermore, tobacco cessation treatment targets only a small percentage of smokers who want to quit. Among cigarette smokers, at any one time, only 10% are prepared to take action toward quitting (i.e., they intend to quit in the next 30 days, (Prochaska and Goldstein, 1991) and only 20% of tobacco users are willing to quit in the next 6 months (Etter et al., 1997). For individuals who are unwilling or unable to quit, alternative methods of treatments or tobacco-like nicotine delivery devices must be considered and tested. Although total abstinence should be the ultimate goal in treatment, for those who are unwilling or unable to quit, reduction may be an important alternative to further decrease the mortality and morbidity associated with smoking (Henningfield and Slade, 1998; Hughes, 1995). The importance of this alternative strategy is highlighted by the dose–response relationship that has been observed between the amount of tobacco consumption and morbidity and mortality (Jimenez-Ruiz et al., 1998; Thun et al., 1995). Similarly, models have been developed showing that reduced smoking may lead to reduced risk premature death (Burns, 1997), although longitudinal studies have not been conducted to date to confirm the results from these models. Therefore, methods to reduce tobacco use or long-term use of products to sustain abstinence require serious consideration.

Harm Reduction Indications for Pharmacological Treatments

The use of medications for harm reduction can be considered in various ways. First, medications can be used to reduce the rate of smoking either as a means toward eventual abstinence or as an end goal. Second, medications can also be used in situations in which the smoker cannot smoke cigarettes and chooses to use a medication, most likely nicotine replacement, to abate craving or withdrawal symptoms. This situational use of nicotine replacement may indirectly lead to reduced smoking, as well. Third, harm reduction may also include long-term maintenance on a medication as a relapse prevention aid and not merely a smoking cessation aid.

Several concerns exist when considering these approaches, particularly when advocating for reduced smoking if smokers are unwilling or unable to quit. One concern that has been raised is the potential for exposure to increased amounts of nicotine beyond those that the smoker normally experiences solely from smoking and the adverse effects that may be experienced when combining smoking with a nicotine replacement. This increased nicotine exposure may have associated toxicity, although the risk depends on the toxicity specific to nicotine, which tends to be confined primarily to reproductive and cardiovascular disorders. Prior studies have examined the use of nicotine replacements with concurrent smoking. These studies have found no major adverse effect even at a very high dose of nicotine patch (Benowitz et al., 1998) or in smokers who

have experienced cardiovascular disease (Joseph et al., 1996; Murray et al., 1996; Working Group for the Study of Transdermal Nicotine in Patients with Coronary Artery Disease, 1994).

A second concern is the reduced desire for abstinence as a result of a reduced perception of risk associated with decreased levels of smoking. Individuals who would normally have quit may choose continuing to smoke at lower amounts. Similarly, the desire to quit may also be decreased if the use of nicotine products is encouraged in areas that restrict tobacco use, so that the individual no longer needs to contend with withdrawal symptoms in these situations. A third and related concern is the reduced perception of risk among adolescents and younger adults. If the option of smoking a few cigarettes with reduced health consequences is available, then perhaps a greater number will be more willing to initiate smoking. A fourth concern, which is related to the long-term use of medications, is the potential toxicity that may be associated with chronic use, even though the toxicity is lower than that of tobacco products. An important principle that underlies all of these concerns is that no increase in harm occurs as a result of using a tobacco exposure reduction approach and that a significant and meaningful decrease in actual harm be the outcome.

Several advantages related to the availability of exposure reduction approaches include potentially increasing recruitment into treatment. That is, smokers who are not ready to quit can perhaps be persuaded to begin to reduce their tobacco consumption as a step toward cessation or as a method to reduce harm. This reduction may then reduce mortality and morbidity among individuals who want to continue smoking, and may also reduce environmental tobacco smoke exposure, and eventually facilitate abstinence. Furthermore, the use of medications in situations where smoking may not be allowed (e.g., work environment) may reduce work-related accidents, which have been observed to increase during periods of tobacco withdrawal (Waters et al., 1998).

Use of Pharmacological Agents for Tobacco Exposure Reduction

The use of nicotine replacements for tobacco exposure reduction has been suggested to minimize compensatory smoking behavior when reducing the number of cigarettes smoked (Shiffman et al., 1998). In addition, nicotine replacements are likely to induce minimal harm since it is the cigarette constituents and pyrolysis products other than nicotine that are primarily responsible for the morbidity and mortality associated with smoking (Benowitz, 1998; Henningfield, 1995). Use of nicotine to reduce smoking is not a new concept. One study observed that half of the smokers prescribed gum at a nonresearch routine outpatient setting reported using gum to help them cut down rather than quit smoking (Johnson et al., 1992). Furthermore, nicotine replacement treatment studies have shown that smokers continue to smoke at a reduced rate in conjunction with using nicotine products (e.g., Transdermal Nicotine Study Group, 1991; Bjornson-Benson et al., 1993).

The effects of administering nicotine intravenously or orally on reducing cigarette consumption were observed in the late 1960s and 1970s (e.g., Jarvik, 1970; Lucchesi et al., 1967). Subsequent short-term, laboratory research studies have demonstrated that nicotine administered intravenously (e.g., Benowitz and Jacob, 1990), by nicotine gum (e.g., Herning et al., 1985; Nemeth-Coslett and Henningfield, 1986; Nemeth-Coslett et al., 1987; Russell et al., 1976), and by patch (e.g., Foulds et al., 1992; Pickworth et al., 1994) reduced smoking behavior, although modestly. This modest reduction may be due to the insufficient doses of nicotine that were administered, short-term treatment, and/or enrolling subjects who were not interested in reducing the number

of cigarettes smoked. In a recent study, Benowitz et al. (1998) examined the use of high-dose transdermal nicotine (TN) on smoking suppression. In a double-blind, crossover design among smokers with no desire to quit, they observed that TN reduced nicotine intake from cigarette smoking by 3, 10, and 40% on average under the 21, - 42 and 63-mg/day conditions respectively. Peak plasma nicotine concentrations were approximately 40, 60, and 70 ng/ml, respectively, versus 28 ng/ml attained with the placebo patch. They concluded by saying that high-dose nicotine has the potential to substantially reduce smoking and thereby harm.

Current studies, which have examined the use of nicotine replacements for the primary purpose of cigarette use reduction, have shown substantial decreases in the number of cigarettes smoked and levels of carbon monoxide (Fagerstrom et al., 1997; Rennard et al., 1990). Rennard et al. (1990) studied the effects of treating smokers with at least 10 pieces of 2-mg gum per day on lower respiratory tract inflammation in heavy smokers. He observed that cigarette consumption decreased by more than one-half (from 51 to 19 cigarettes per day) and carbon monoxide was similarly reduced (from 49 to 27 parts per million [ppm] after a 2-month period). Furthermore, lower respiratory tract inflammation in these heavy smokers was significantly improved.

Fagerstrom et al. (1997) conducted a crossover study in which dependent smokers had a choice of either 2-mg nicotine gum, a nicotine patch, nasal spray, and 2-mg oral tablet or were assigned to a product for 2 weeks. This study showed that compared to baseline, there were a 54% reduction in smoking, 35% reduction of CO, and 32% reduction of withdrawal symptoms. About 59% reduced smoking by more than 50%, and 5% smoked no cigarettes at the end of the 4-week intervention period. The highest mean cotinine concentration attained during treatment was 373 ng/ml compared to 360 ng/ml obtained during the screening period. Fagerstrom and associates concluded that a "smoking reduction procedure may help the very recalcitrant smoker gain confidence and increase the control of his/her smoking behavior."

Bolliger et al. (2000) examined the effects of the nicotine inhaler in reducing smoking among smokers who were unwilling or unable to stop smoking immediately ($N = 400$) in a double-blind, placebo-controlled 4 month trial with a 2 year follow-up. Participants were allowed access to the inhalers for up to 18 months. At the end of the 4-month trial, significantly greater numbers of participants assigned to the active group (26%) were able to sustain reduction (reduced smoking by at least 50% from week 6) compared to the placebo condition (9%). This significant difference continued to be observed at 24 months (9.5% vs. 3.0%, active vs. placebo). Significant differences in reduction in carbon monoxide were observed between active and placebo inhaler conditions at 6 weeks (68.4% vs. 84.1% of baseline, respectively) and 4 months (58.3% vs. 71.1% of baseline, respectively). About 10% of the population was abstinent at the 2-year follow-up. No serious adverse events related to treatment occurred during the study. The authors concluded that sustained reduction in smoking can be achieved using the nicotine inhaler. Recent studies have examined the effects of short-term use of the nicotine patch on reducing cigarette consumption among psychiatric patients who are not interested in quitting. These studies have observed reductions in cigarette consumption ranging from 20 to 42% (Dalack and Meador-Woodruff, 1999; Hartman et al., 1989; Hartman et al., 1991), with the greatest reductions observed among the heaviest smokers (Dalack and Meador-Woodruff, 1999). Reduction approaches with psychiatric populations may be beneficial.

Other Harm Reduction Strategies Associated with Medication Use

Nicotine replacement agents, used on an ad libitum basis, can be used under circumstances in which smoking is not permitted (e.g., restaurants, airplanes, smoke-free workplaces). Nicotine replacements have been shown to reduce craving as well as withdrawal symptoms (Hughes et al., 1989) and therefore may be beneficial in situations where a smoker cannot smoke. Long-term maintenance of medications may also be considered a harm reduction strategy, similar to methadone use among individuals addicted to opiates. Few studies have examined the long-term use of nicotine replacement products to sustain long-term abstinence.

One study was the Lung Health study in which nicotine gum was available up to 6 months, but approved for longer use if deemed necessary. Nicotine gum was dispensed in the context of 12 weeks of cognitive behavioral smoking cessation treatment. The results showed a 5-year sustained smoking cessation rate of 22% in this intervention group versus 5% in the usual care group (Kanner et al., 1999). An ancillary examination of the data focused on long-term gum use in this population (Bjornson-Benson et al., 1993). Among participants enrolled in the study, 28.9% were using gum at 12 months since study entry. About one-third of the sustained nonsmokers, over one-half of intermittent smokers, and one-fifth of continuing smokers were using gum at 12 months. This rate of long-term gum use among nonsmokers is consistent with other studies that showed rates of use around 22% at one year (Hughes, 1998). As an added note, in the Lung Health Study, continuing smokers not using nicotine nicotine gum (12.4 vs. 23.5 cigarettes per day). No adverse effects were observed, although among sustained nonsmokers, continuous gum users reported more mild side effects than intermittent gum users.

Recently, a trial has been conducted examining the use of bupropion for at least 1 year as a relapse prevention agent (Hays et al., 2000). All smokers enrolled in the trial were assigned to bupropion SR for a period of 7 weeks. Those smokers who were abstinent at the end of 7 weeks were randomly assigned to bupropion SR or placebo for 48 weeks. Subjects assigned to the bupropion group had greater success in maintaining abstinence compared to those assigned to the placebo at the end of the 78-week follow-up (47.4% vs. 37.7%, respectively).

Summary and Recommendations.

In summary, the results show that nicotine replacements are effective in reducing smoking on a short-term as well as a long-term basis in some smokers. The availability of a reduction or controlled smoking approach does not seem to deter individuals from becoming abstinent. Furthermore, high doses of nicotine do not seem to cause acute adverse events even among smokers who have experienced cardiovascular disease. Long-term use of nicotine replacements may also be effective in sustaining abstinence and is less toxic than a relapse to smoking. There is a great need for large and long-term clinical trials to determine whether different pharmacological agents, including products other than nicotine replacements, can lead to prolonged and significant reductions in smoking and less harm to individuals. Included in potential medications to be examined are some antidepressants, antagonists and medications that alter the metabolism of nicotine. Finally, these treatment methods must be considered carefully for special populations of smokers, including adolescents, individuals with comorbid conditions or medically compromised individuals, and pregnant women.

OTHER POTENTIAL HARM REDUCTION METHODS: BEHAVIORAL STRATEGIES AND TOBACCO CONTROL POLICIES

Altering tobacco products and using pharmacological agents to reduce smoking are not the only methods of harm reduction. Behavioral methods and tobacco control policies have also led to reduced smoking. These approaches have to be considered so that the pharmacological approaches aimed at reducing an individual's smoking behavior can be complemented or augmented by behavioral and public policy approaches. Furthermore, changes in tobacco products aimed at reducing toxicity must be marketed only in the context of a comprehensive tobacco control policy whose primary goals are prevention of smoking initiation and total cessation of smoking. The normative belief that any tobacco use is harmful must be maintained (IOM, 2000).

Harm Reduction Using Behavioral Methods

Even as early as the 1970s, researchers observed that a significant "number of habitual smokers reported that they wanted to give up smoking but found it extremely difficult to reduce their rate of smoking or quit entirely" (Shapiro et al., 1971). This observation led to a number of studies using behavioral interventions aimed at reducing smoking. The behavioral means for achieving a reduction in smoking included smoking at fixed intervals and increasing the intervals between cigarettes; smoking a cigarette only when signaled to smoke (e.g., Levinson et al., 1971; Shapiro et al., 1971); changing smoking behavior, such as taking shorter puffs, reducing the number of puffs, and reducing the percentage of the cigarette smoked (e.g., Frederiksen and Simon, 1978; Glasgow, et al., 1983); contingency contracting (Frederiksen and Peterson, 1976), and eliminating smoking in specific situations (e.g., Foxx and Axelroth, 1983; Glasgow, 1978). In addition, although they represent more of a pharmacological than a behavioral approach, gradually lowering the nicotine content in cigarettes (e.g., Foxx and Brown, 1979; Prue, et al., 1981) and graduated filters (McGovern and Lando, 1991) have also been used as methods for reducing nicotine. All of these methods have shown some degree of success in reducing the number of cigarettes smoked, with concomitant reductions in extent of nicotine exposure. Two studies have compared the effects of a behavioral intervention of cigarette reduction versus a waiting list control. Each study had a goal of reducing cigarettes by 50% of baseline using a variety of behavioral techniques. In one study, although only 60% of the original sample remained in the program, these smokers achieved a median reduction of 75% compared to a 2% reduction in the waiting list control group at the end of the 8-week treatment period (Shapiro et al., 1971). Furthermore, 6 weeks after the termination of treatment, the median reduction was 43%. In the other study, a combination of treatment techniques, with and without feedback on carbon monoxide levels, was used sequentially over 5 weeks: changing brands to machine-measured low-tar and nicotine cigarette, reducing the number of cigarettes, and reducing the percentage of the cigarette smoked (Glasgow et al., 1983). Significant treatment effects were observed at he end of treatment when comparing the waiting list control with controlled smoking treatment groups. In general the results showed a mean reduction of 56% in the nicotine content of cigarettes, 28% in the number of cigarettes, and 19% in the percentage of cigarette smoked in the controlled smoking conditions.

Studies have also been conducted to determine long-term maintenance of reduced smoking and the rate of cessation attempts among these individuals. Hughes et al. (1999) examined whether cigarette smokers can significantly reduce and sustain reduction by analyzing longitudinal data from subjects involved in the Community Intervention Trial for smoking cessation. He

observed that at the 2-year follow-up, 17% had decreased smoking by 5–25%, 15% by 24–49%, and 8% by 50% or more. Among smokers who reduced their smoking (≥ 5%) at 2 years, 52% reported maintaining this reduction at 4 years. In addition, these investigators found that decreased smoking did not predict an increase or decrease in quit attempts or abstinence, indicating that reduction does not seem to promote or deter cessation.

One study indirectly assessed maintenance of reduction and rate of cessation by conducting a 3–4-year follow-up among smokers who had enrolled in a smoking cessation program (Colletti et al., 1982). About one-third of the smokers who were unable to achieve abstinence, but smoked less than or equal to 50% of baseline smoking at posttreatment, maintained this rate at 1-year follow-up. This maintenance rate declined to about 13–18% at 3–4 year follow-up. However, 18–20% of the smokers achieved abstinence. Therefore, among those who had reduced smoking at posttreatment, about 33–36% were able to quit or sustain the reduction for 3–4 years. These results would suggest that a lower smoking rate can be sustained and does not necessarily discourage cessation attempts.

Glasgow et al. (1985) directly examined these issues by conducting a 2½-year follow-up in 48 subjects enrolled in a controlled smoking program rather than a cessation study. The results indicated that 9% became abstinent and 9–36% showed some improvement on various reduced smoking behavior parameters from posttest to follow-up. These results would suggest that further tobacco exposure reduction can occur in about a third or more of the population. In addition, the smoking cessation rate is no lower than that observed among a general population of smokers or general practice intervention with smokers. In a later study, Glasgow et al. (1989) explored how an abstinence-based program, in which smoking was not condoned after the quit date, compared to a program in which participants had the option of complete smoking cessation or controlled smoking. No significant differences in smoking cessation rates were observed between the two conditions at either posttest or 6 months. This result would indicate that allowing controlled smoking among those who want to quit does not necessarily lead to either less interest in abstinence or a promotion of abstinence. In a review article (Hughes, 2000) also concluded that smokers can sustain reductions in smoking, and reductions in smoking do not undermine cessation.

More recent exploration of reduced smoking has used computerized devices to gradually wean smokers from cigarettes as a means to achieve cessation. One computerized program, Lifesign Computer Assisted Smoking Program, involves a scheduled reduction by increasing the interval between cigarettes and informing individuals when to smoke. The scheduled time-interval approach seems the most promising of the behavioral treatment methods based on studies by Cinciripini and colleagues (Ciniciripini et al., 1995 and 1997) compared to abrupt cessation or nonscheduled reduction of cigarettes. This behavioral method systematically reduces the level of nicotine exposure, disrupts habitual smoking patterns, and gives smokers the opportunity to develop new behaviors or skills in response to cues associated with smoking.

Summary and Recommendation.

In summary, the results from these studies show that smokers can reduce their smoking rate using behavioral methods, that this rate can be sustained over time, and that reduced smoking does not necessarily compromise cessation efforts. However, more systematic studies focused directly on these issues should be conducted. Furthermore, tobacco addiction involves more than a physical addiction to nicotine, but also behavioral and psychological aspects that also need to

be targeted in exposure reduction as well as cessation. Rigorous studies combining behavioral and pharmacological methods for reduced smoking have yet to be conducted. For example, the use of pharmacological agents may have to be embedded in effective behavioral treatment methods to maximize tobacco use reduction and maintain this reduction.

Harm Reduction Using Environmental Methods

Although not directly considered a harm reduction approach, comprehensive tobacco control policies have clearly lead to a reduction in the overall consumption of cigarettes, including smoking intensity (e.g., Institute of Medicine National Research Council, 2000; Pierce, et al., 1998). Increasing taxes or the price of cigarettes has uniformly reduced their overall consumption (IOM 2000), with a 10% increase in price resulting in a 4% decrease in total consumption of tobacco. Price elasticity, that is, the degree of responsiveness of demand to price change, may be greater among youth than among older adults. Increased cigarette prices lead to significant reductions in the quantity smoked by youthful smokers as well as a reduction in participation in smoking (Chait, 1994; Chaloupka and Wechsler, 1995; Lewit et al., 1981; Tauras and Chaloupka, 1999). Increased taxes on smokeless tobacco also result in a reduction in the amount used as well as the frequency of use (Chaloupka et al., 1996).

Work place smoking restrictions have also significantly reduced the consumption of cigarettes (IOM 2000). This reduction includes the intensity of smoking among employees as well as increased quit rates (e.g., Brownson, et al., 1997; Evans, et al., 1996; Glantz, 1997; Glasgow, et al., 1997; Tauras and Chaloupka, 1999). In one study, the number of cigarettes smoked per day was not significantly different between work sites with restrictive versus unrestrictive smoking policy in a cross-sectional analysis. However, in a longitudinal analysis, work sites that initially had unrestrictive smoking policies but changed to restrictive policies showed reduced smoking compared to those that continued unrestrictive smoking policies (Jeffery et al., 1994). A 10% decrease in smoking was observed in this study, which is similar to if not lower than the reduction in number of cigarettes reported in other studies (Evans et al., 1996; Farrelly et al., 1999).

In another study, smokers who worked in places where the smoking ban was total or partial smoked five fewer cigarettes during the work days than leisure days. No differences were observed in the consumption of cigarettes between work days and leisure days in smokers who were employed in places with no smoking bans (Wakefield et al., 1992). These results were found across all occupational status groups. Reduced work day smoking, 18 months after the initiation of a total ban on smoking in the workplace, was found among 32.3% of smokers, and generalization to nonworkdays occurred in some smokers (Borland et al., 1991).

Another study showed that a greater number of daily smokers were light smokers (<15 cigarettes per day) if they worked in a smoke-free environment and if they lived in a home in which there was a partial or total ban on smoking (Farkas et al., 1999). Among young smokers, limits on smoking in schools and restrictions in public places led to a reduced number of cigarettes consumed (Chaloupka and Grossman, 1996; Chaloupka and Wechsler, 1995). Furthermore, schools that have comprehensive policies, including a high emphasis on prevention education, resulted in lower amounts of smoking by smokers than schools that had less comprehensive policies (Pentz et al., 1989).

Other tobacco control policies include tobacco advertisement bans and limiting access of adolescents to tobacco products. While a limited set of tobacco advertising restrictions have no effect on tobacco consumption, comprehensive tobacco advertising bans have reduced tobacco consumption by more than 6% and counter advertising by 2% (Saffer and Chaloupka, 1999).

Whether these bans have any effect on the number of cigarettes smoked is unclear. Limits on the availability of tobacco products to underage youths have no impact on college students (Chaloupka and Wechsler, 1995) and adolescents or youth, which may be a function of poor enforcement of these restrictions (Chaloupka and Grossman, 1996; Rigotti et al., 1997). Other studies show that enforcement of youth access restrictions does reduce tobacco consumption (IOM, 2000). Strong limits on youth access to smokeless tobacco, however, have been observed to reduce the frequency of use of this product (Chaloupka et al., 1996).

Summary and Recommendations.

In summary, individual harm reduction strategies must occur in the context of public policy of tobacco control if a significant reduction in death and disease is the primary goal. These policies would set the normative standard that tobacco use is highly discouraged. Other issues that require careful consideration are the cost and availability of products. The costs of pharmacological agents that have less associated toxicity are much higher per unit of purchase than those of the more highly toxic tobacco products. Furthermore, tobacco products are more readily available at a number of outlets than pharmaceutical products. The impact of availability, even within the area of pharmaceuticals, is highlighted by a study showing increased quit attempts among smokers when the nicotine patch was released and when nicotine gum and the patch went over the counter (CDC, 2000). The rate of these quit attempts was sustained with the advent of OTC products rather than the introduction of new products. Therefore, if a significant impact is to be made on the negative consequences associated with tobacco use, then the safer nontobacco products must be made more available to consumers who are already addicted to nicotine, whereas the more toxic tobacco products must be made less available.

General Conclusive Statements.

Harm reduction is not a new concept, but it is a controversial one, in part because of the previous history with low-tar and nicotine cigarettes. Evidence exists showing that "light" cigarettes may have lead to compensatory smoking behavior and therefore no reduction in harm. Furthermore, many smokers of these light cigarettes believed that they were reducing harm, and this perception may have undermined cessation attempts (Cohen, 1996; Kozlowski et al., 1998). These observations led to recommendations for principles that should be followed to determine the feasibility and effectiveness of tobacco exposure reduction approaches (Henningfield and Slade, 1998). Some of the these principles that should be considered include the following: (1) reduction of exposure to toxins with verification based on biomarkers; (2) no reduction in cessation attempts; and (3) no increased safety risk.

Various methods to reduce harm have been proposed. These include changing tobacco products themselves by adding filters, reducing tar and nicotine, via ventilation, or maintaining nicotine but reducing tar (e.g., reducing tobacco nitrosamines, controlled tobacco burning). Other approaches include reducing tobacco consumption, by use of either pharmacotherapies, behavioral strategies or polices that restrict access to tobacco products. In addition, long-term use of pharmacotherapies to substitute for tobacco use has also been advocated. Examination of harm reduction products and approaches will present a number of issues such as (1) the extent to which reduction of exposure to tobacco toxins must occur before beneficial effects are observed and treatment can be considered a success, that is, how to define a successful treatment outcome; (2) the length of the follow-up or type of surveillance necessary to monitor for any adverse effects;

(3) valid and reliable indices for reduction of tobacco toxins; (4) methods to market and position this approach without compromising the message of abstinence as the primary goal and without increasing the initiation of using tobacco products; (5) the cost-effectiveness of this approach; (6) the willingness of health care providers to advise and assist patients who are reluctant to quit in using this technique if reduction in risk is observed as a result of reduction in toxic tobacco exposure; (7) whether nicotine-containing tobacco products should ever be touted by the tobacco industry as a way to quit smoking or reduce its health consequences; and (8) the industry's positioning of pharmaceutical products and tobacco-containing products with less toxins, especially when the differences between them tend to become blurred. In clinical trials, the issue may arise as to how to identify individuals who are unwilling or unable to quit, that is, the criteria to be used to make this determination as well as how and when to intervene with smokers, who use PREPs, to help them eventually achieve abstinence. Finally, a number of regulatory issues will have to be addressed.

REGULATION OF EXPOSURE REDUCTION PRODUCTS

Drugs

The regulatory system in the United States for therapeutic drugs, administered by the Food and Drug Administration, is the most stringent regulatory system in our society for new products. The scientific, legal, and administrative features of this system have been described in many publications, but a particularly good review for the purposes of this report is that of Page (Page 1998).

The Food, Drug and Cosmetic Act requires affirmative approval of all new drugs by the FDA before marketing. The scientific information required to support such approval includes proof of the identity and structure of the active ingredient(s); detailed information on the composition of the formulation (e.g., tablet, capsule, solution); reports of toxicology studies in animals, including carcinogenicity and reproductive toxicology when necessary; clinical pharmacology studies in humans to show the pharmacokinetic (blood-level) profile and potential for interactions with other drugs; and most importantly, at least two controlled clinical trials in humans demonstrating the effectiveness of the drug for the claimed indication and an acceptable side-effect profile (21 CFR 314). This information is summarized in the product labeling for the physician in a leaflet popularly known as a package insert. This labeling also serves as the basis for regulating promotion and advertising after marketing.

In addition, all clinical studies in humans sponsored by drug manufacturers are subject to regulatory oversight under the Investigational New Drug (IND) regulations (21 CFR 312). This oversight includes review of each protocol by the FDA and by an institutional review board, submission of periodic reports, and prompt submission of serious adverse events that occur during clinical studies.

After marketing, the manufacturer must continue to submit to the FDA reports on new and unexpected adverse events, changes in manufacturing or formulation, changes in labeling (e.g., new warnings), and new advertising materials. Manufacturing plants are also subject to periodic inspection to ensure compliance with good manufacturing practices. This regulatory system serves to promote public trust in the quality, effectiveness and truthful labeling of medicinal products and also makes the pharmaceutical and biotechnology industries among the most heavily regulated businesses in our society.

Essentially all new drugs are first approved as prescription drugs. In time, however, some may be switched to over-the-counter status and be sold directly to consumers. OTC drugs are subject to the same regulatory requirements as prescription drugs except that the regulation of their advertising is under the authority of the FTC rather than the FDA. The tests for determining whether a drug can be sold OTC are (1) whether it can be labeled for use by the consumer without the need for a physician and (2) whether it is safe and effective for OTC use. The FDA has historically limited the use of OTC products to symptomatic conditions such as colds, heartburn, and headaches that can be diagnosed without the need for a physician. Furthermore, to promote safe use, the FDA has typically approved for OTC use only drugs of low inherent risk such as antacids and sunscreens or, in the case of drugs that are potentially toxic such as nonsteroidal anti-inflammatory agents and antihistaminics, lower doses than are available by prescription. Drugs with sufficient abuse potential to be scheduled under the Controlled Substances Act cannot be offered OTC.

The only nicotine-containing products currently approved by the FDA for OTC use are Nicorette™ gum, Nicoderm CQ patch, and Nicotrol™ patch. The FDA decision to permit these products to switch from prescription to OTC status required discussion at two meetings of the Non-Prescription Drug Advisory Committee before action was taken. A later decision to permit mint-flavored Nicorette™ gum also required considerable time and discussion. The concerns raised in these discussions were whether these products would actually be effective in an OTC setting without accompanying professional intervention and whether increased abuse and/or cardiovascular risk might develop. Subsequent experience has been reassuring on all counts (Hughes et al., 1999).

Nicotine-containing drugs are currently approved by the FDA only to reduce withdrawal symptoms as an aid in smoking cessation. Their labeling clearly states that the goal of treatment is cessation of smoking and subsequent withdrawal from the nicotine containing tobacco product. The labeling of the prescription products advises against chronic use beyond 6 months and over the counter labeling advises against long-term use while continuing to smoke or use other nicotine-containing products. Although use as part of a comprehensive behavioral smoking cessation program is encouraged, there is no information in the labeling of nicotine-containing products about their effectiveness in combination with other programs or Zyban™ (bupropion SR). In contrast, the labeling for Zyban™ the only other drug approved as an aid for smoking cessation, notes an additive effect in combination with the nicotine patch and advises that Zyban™ may be continued indefinitely in successfully treated patients. Long-term use of these products with cigarettes, which might occur in a harm reduction strategy, is discouraged by the approved labeling.

The other prescription drugs reported to be useful for smoking cessation—clonidine, nortriptyline, and mecamylamine—are not approved by the FDA for this indication. That does not limit the ability of physicians to prescribe them for this use (Temple), but it does prohibit manufacturers from promoting them for this use.

Medical Devices

The modern regulatory framework for medical devices derives from the Medical Device Amendments of 1976 to the Food, Drug and Cosmetic Act. This legislation defines a medical device as an "instrument, contrivance or similar article intended to affect the structure or any function of the body" and requires the FDA to classify all medical devices according to their degree of risk (Page, 1998). Class I devices are those of low risk such as crutches and bandages that

need meet only general standards. Class II devices are envisioned in the law as devices of intermediate risk that need specific performance standards to ensure their safety and effectiveness. Because performance standards can be established only by regulation and the process is time-consuming and burdensome, this provision of the law has seldom been used. Class III devices are those of highest risk, such as heart valves and pacemakers, and require preclearance by the FDA before marketing.

The device laws have never been applied by the FDA to any therapeutic product intended for smoking cessation. Although the containers for the Nicotrol™ Inhaler and Nicotrol™ Nasal Spray may look like devices, they are regulated by FDA as the packaging for a drug and not as medical devices.

In 1996, the FDA claimed regulatory authority over cigarettes and smokeless tobacco products on the grounds that a cigarette is a medical device intended to deliver the drug nicotine. This resulted in extensive litigation between the FDA and the tobacco industry, the details of which are included in the next section.

Tobacco Products

The effort to regulate tobacco has a long history (Jacobson and Wasserman, 1997; Kluger, 1996). By the beginning of the twentieth century, there was an important antitobacco movement in the United States based on the conviction that tobacco use was immoral, uncouth, and corrupting. Many states passed laws prohibiting the production, sale, or use of cigarettes. Smoking, especially by women, was discouraged, and female smoking was equated with low moral character. A few states also banned the sale of tobacco to minors in an effort to combat the "demoralizing" effect of tobacco on children. These state laws, however, were poorly enforced and were eventually overturned as smoking became much more popular during the Great Depression and World War II.

Beginning in the 1930s, the scientific community began linking smoking directly to disease. This evidence mounted in the 1940s and 1950s, culminating in 1964 in the landmark Surgeon General's report (PHS, 1964) outlining the adverse health effects of smoking in terms of cancer, heart disease, and lung disease. Later Surgeon General's reports considered such topics as the adverse health effects of environmental tobacco smoke (U.S. DHHS, 1986), the problem of adolescent smoking (U.S. DHHS, 1994), and tobacco use by minorities (U.S. DHHS, 1998). In response to the 1964 Surgeon General's report, Congress passed the Cigarette Labeling and Advertising Act of 1965, which forced cigarette manufacturers to place the warning, "Caution: Cigarette smoking may be hazardous to your health," on all packaging. This act, however, prevented the states and the FTC from enacting their own rules requiring more explicit warnings on packaging.

In 1969, Congress enacted the Public Health Cigarette Smoking Act, which banned all cigarette advertising on television and radio and modified the warning labels to read, "Warning: The Surgeon General Has Determined That Cigarette Smoking Is Dangerous to Your Health". This law negated a decision by the Federal Communications Commission that would have required, under the "Fairness Doctrine", stations broadcasting tobacco ads to provide equal air time to antitobacco public messages because it also prohibited broadcast advertising of cigarettes after January 1, 1971. In 1972, the FTC began requiring cigarette manufacturers to display a warning label on all cigarette advertising. Further changes in the health warnings came in 1984 and 1986 through the Comprehensive Smoking Health Education Act and the Comprehensive Smokeless Tobacco Health Education Act, respectively, which required the rotation of four specific warn-

ings on cigarette and three rotating warnings smokeless tobacco packaging and advertising (Jacobson and Wasserman, 1997)

Comprehensive federal tobacco regulation has been limited by the exemption of tobacco from numerous federal acts designed to protect the public from harmful products, including the Controlled Substances Act of 1970, the Consumer Product Safety Act of 1972, and the Toxic Substances Control Act of 1970. The Food, Drug and Cosmetic Act (FDCA), however, is silent with respect to tobacco products and thus stands as a potential regulatory tool for any product, tobacco containing or not, that makes an explicit health claim and also meets the definition of a drug or device. In the 1950s the FDA exerted jurisdiction in two cases in which tobacco companies made explicit claims regarding the health benefits of their products. In 1953, the FDA classified Fairfax cigarettes as drugs when the manufacturer enclosed leaflets with language that implied effectiveness in preventing an array of diseases, and in 1959 (United States v. 354 Bulk Cartons Trim Reducing-Aid Cigarettes), the FDA successfully prohibited explicit claims of weight reduction by a cigarette. During the late 1970s, however, when Action on Smoking and Health (ASH) and others petitioned the FDA to assert jurisdiction over cigarettes as drugs and devices, the FDA denied the petition on the grounds that cigarettes did not fall under the statutory definition of a drug. The FDA asserted that evidence of consumer intent to use the product predominantly for the health effects or the effects on the structure or function of the body was not sufficient to infer a similar intent by the manufacturers. Tobacco manufacturers appeared to be free from more comprehensive regulation as long as they did not make explicit claims about health benefits or effects on body structure or function and if they complied with advertising and labeling restrictions enacted by Congress (U.S. DHHS, 2000; Slade and Ballin, 1993).

In 1988, the Coalition on Smoking or Health (CSH) and others petitioned the FDA to classify low-tar and nicotine products as drugs and to classify the new smokeless cigarette product by RJR, "Premier", as an alternative nicotine delivery system and, hence, subject to regulation as a drug. CSH cited indirect claims made through advertising and marketing as evidence of the manufacturer's intent to have the product used for the mitigation or prevention of disease (Slade and Ballin, 1993). Again in 1994, the FDA was petitioned by CSH to classify all cigarette products as drugs as defined in the FDCA. Later that year, the FDA Commissioner announced in a letter to CSH and later in congressional testimony that the FDA, in light of new evidence, would revisit the FDA's authority to regulate tobacco products as drugs and devices as defined in the statute.

Following this investigation, the FDA asserted its jurisdiction and proposed regulation of certain tobacco products in the Federal Register in August 1996. The authority for such regulation was based on new evidence showing that cigarettes and smokeless tobacco products are nicotine-containing (i.e., drug-containing) devices as defined by the FDCA of 1938. The FDA determined that nicotine could be classified as drug based on the facts that (1) nicotine causes and sustains addiction, (2) nicotine produces other psychoactive (mood-altering) effects, and (3) nicotine controls weight. The definition of nicotine as a drug as defined by the FDCA includes an intent by the manufacturer for the product to be used as a drug in the bodies of their customers.

The FDA's assertion that cigarettes and smokeless tobacco products may be defined as nicotine delivery devices was based on findings that (1) the effects of nicotine are so widely known that it is foreseeable to a reasonable manufacturer that these products will cause addiction and other pharmacological effects and will be used by the consumers for these effects and to sustain the addiction; (2) consumers use tobacco products mainly to sustain addiction, for the mood-

altering effects, and for weight loss; (3) manufacturers of tobacco products know that nicotine has pharmacological effects and that consumers use their products primarily to obtain the pharmacological effects of nicotine; (4) manufacturers design their products to provide consumers with a pharmacologically active dose of nicotine; and (5) as a consequence, consumers keep using cigarettes and smokeless tobacco to sustain their addiction to nicotine (61 Fed. Reg. 1996). The agency disclosed new evidence from industry documents of product engineering, nicotine delivery manipulation, and industry research in support of its contention that tobacco products are intended to change the structure or function of the body. This provided the rationale for the FDA's proposed new rules on the advertising, marketing, and sale of tobacco. Many of the proposed actions were directed toward limiting the access of minors to tobacco products and stopping cigarette advertising and promotion targeted at adolescents.

Specifically, the new regulations imposed a ban on the sale of tobacco products to minors; required vendors to check for proof of age; banned cigarette vending machines, banned billboard or other advertisements easily accessible to youth; restricted all advertising to black and white text (except in publications read primarily by adults); banned tobacco manufacturer sponsorship of sporting and entertainment events; banned promotional items displaying a brand name, logo, or free samples; and required tobacco industry financial support for antitobacco education for children (U.S. DHHS, 2000).

On August 23, 1996, after soliciting public comment, the FDA published its final rule, modified only in that adult-only businesses were exempted from certain restrictions. The FDA was met by legal action from the tobacco industry, advertising industry, and tobacco vendors to block implementation of these rules. The case was initially heard by the federal district court in Greensboro, North Carolina (April 1997), which upheld the FDA's regulatory authority over tobacco products and supported the FDA definition of tobacco products as combination drug and drug delivery devices. The court, however, ruled that the FDA had no statutory authority to regulate tobacco advertising or promotion.

The decision was appealed by both sides in August 1997, and in August 1998, the Fourth Circuit overturned the district court decision and revoked FDA's proposed authority to regulate tobacco products. The court found that if cigarettes and smokeless tobacco were under FDA jurisdiction as outlined by the proposed regulations, the agency's only choice would be to ban the products in light of their known dangers to health. Any other consideration would not be within the scope of FDA's regulatory powers. The court concluded that Congress did not intend the FDCA to be used for the regulation of tobacco products and that Congress has never equipped the FDA with the power to regulate tobacco products. This decision was upheld by the Supreme Court on March 21, 2000. The majority opinion stated that the FDA's regulatory actions were incongruous with what was intended by Congress and that Congress has historically denied FDA the authority to regulate traditional tobacco products.

It is important to recognize that this recent Supreme Court decision in no way limited the authority of FDA to regulate any product, tobacco containing or not, that makes an explicit health claim that would bring the product under the definition of a drug or device. For example, an exposure-reducing claim for a smokeless tobacco product, to the effect that it (like nicotine patches) promotes cessation of smoking, could be judged by the FDA as a drug claim requiring approval under a new drug application. Similarly, the newly emerging set of smoked nicotine-containing products is not necessarily excluded from FDA regulatory authority by the recent Supreme Court decision. An interesting consequence of the current regulatory situation is that a tobacco manufacturer may not be able to make a legitimate exposure-reducing or reduced-risk

claim for a new product, even if truthful, without bringing the product under the jurisdiction of the FDA.

It is also important to note that as a result of the Supreme Court's decision overturning FDA jurisdiction, all current regulatory provisions over tobacco relate only to labeling, promotion and advertising, and taxation. None relate to the technical or scientific standards required of new products or to product safety. Unlike pharmaceutical or device manufacturers, cigarette manufacturers may introduce new curing, blending, and manufacturing techniques into tobacco products without regulatory oversight of any kind. Similarly, new additives, new filters, new aeration mechanisms, new papers, and new constituents may be introduced without regulatory scrutiny. Neither the extent nor the results of toxicology testing of new ingredients in animals are known outside the manufacturer. The effects of new product design and of changes in constituents on the composition of inhaled smoke are not reported to any health authority. Clinical studies on new products are conducted without regulatory oversight over protocols (except for institutional review board review) or review of the results. Once research and development on a new product has been completed, the product is marketed based on the manufacturer's responsibility, again without regulatory review. Manufacturers are under no regulatory obligation to conduct post-marketing epidemiological studies or to collect and report adverse events.

The contrast between the regulatory systems for drugs or devices and for tobacco has been discussed by a number of authors (Henningfield, and Slade, 1998; O'Reilly, 1989; Page, 1998; Slade, and Henningfield, 1998; Warner, et al., 1997), who point out the paradox of a stringent regulatory system for exposure reduction products developed by the pharmaceutical industry and a weak regulatory system for exposure-reduction products developed by tobacco manufacturers. Table 4-8 illustrates the problem.

Table 4-8 Comparison of Two Nicotine Inhalers

Feature	**Eclipse™ (tobacco company)**	**Nicotrol™ Inhaler (pharmaceutical company)**
Operation	Heat source volatizes nicotine and glycerol, and scorches tobacco	Ambient air passing through nicotine reservoir volatizes nicotine
Dose	Mimics cigarettes (lung delivery of nicotine)	Similar to low Nicorette™ dose (buccal delivery of nicotine)
Projected abuse liability	High	Low
Contaminants	High CO, acrolein, "soot," and other contaminants	Not allowed
Claims or Indications	Reduced delivery (unproven to FDA)	Smoking cessation (FDA-approved studies)
Intent	Cause and sustain dependence	Treat dependence
Cost	More than $3.00 per pack of 20 ($0.15 each)	$55.00 per pack of 42 ($1.30 each)
Modification oversight	Modified to be more palatable (and more toxic) without approval	Any modification requires FDA approval

Premarketing approval data	None submitted to FDA	Conventional new drug application submission and FDA approval
Availability	Over the counter	Prescription only

SOURCE: Slade and Henningfield. *Tobacco Product Regulation: Context and Issues*, 53 Food and Drug Law Journal (Suppl.) 43, 61 (1998). Reprinted with Permission of the Food and Drug Law Institute.

Chapter 7 of this report discusses the principles of a science-based regulatory system for tobacco products, including those with exposure reduction or risk reduction claims.

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